OPTIMIZATION OF PHYSIOLOGIC NOISE CORRECTION IN
FUNCTIONAL MAGNETIC RESONANCE IMAGING

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

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2009

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ABSTRACT

Though in widespread clinical and research use as a tool to evaluate brain function, functional magnetic resonance imaging (FMRI) data is severely contaminated by noise, due in large part to physiologic noise caused by respiratory and cardiac variations over time. This dissertation attempts to better characterize several physiologic noise correction techniques applied to pain FMRI data. Three studies are described that collectively work toward determining an optimal physiologic noise correction algorithm to be used in future pain FMRI studies.

First, a novel algorithm, RetroSLICE, is described that uses linear regression to correct acquired images for signal intensity fluctuations correlated to measured respiratory, cardiac, and capnometry variations. The impact of this technique was assessed for a 1.5 T pain FMRI experiment. Each physiologic noise regressor used as a part of the RetroSLICE algorithm independently resulted in a decrease in timecourse variance and an improvement in model fit. Combined correction for the instantaneous effects of respiratory and cardiac variations caused a 5.4% decrease in signal variance and increased model fit (mean $R^2$) by 65%. The addition of ETCO$_2$ correction as part of the general linear model led to 39% further improvement in model fit. Each of these corrections also caused changes in the group activation map.
Next, an optimal transfer function between ETCO$_2$ level and BOLD signal changes was empirically determined using FMRI data in which paced breathing forced a 35% decrease in ETCO$_2$. ETCO$_2$ data convolved with this optimized response function was compared to another measure, the respiratory volume over time (RVT) convolved with an optimized respiration response function. When regressed against FMRI data collected during a breathing modulation task, ETCO$_2$ was more strongly and diffusely correlated to the data than RVT. Conversely, when the same comparative analysis was performed on pain FMRI data, RVT was more strongly correlated than ETCO$_2$. In both cases, allowing ± 2 s flexibility in the response function peak times did not change the relative correlation to the MR data of the ETCO$_2$ compared to the RVT timecourses.

Finally, the well-known physiologic noise correction algorithm, RETROICOR, was implemented on pain FMRI data collected at 1.5 and 3.0 T. Respiratory and cardiac correction with Fourier series phase fitting caused an 8.2% decrease in signal variance and a 227% increase in model fit at 1.5 T, indicating performance superior to RetroSLICE. At 3.0 T, significantly greater improvements were seen: a 10.4% decrease in signal noise and 240% increase in mean R$^2_a$. ETCO$_2$ correction applied with the optimized response function previously determined caused insignificant changes in noise reduction and model fit. Further exploration of the properties of the RETROICOR algorithm showed no difference in impact when applied with physiologic input data sampled at a much higher rate or when accounting for the interleaved slice acquisition order. These findings suggest that RETROICOR should be included as a part of the physiologic noise correction procedure in pain FMRI studies at 1.5 and 3.0 T.
To my family and friends,
for their patience, love, and support
during the years over which
this work was done.
ACKNOWLEDGMENTS

The work presented in this dissertation could not have possibly been performed by one person working in isolation. The journey to the completion of this project has involved contributions both small and large from many people to whom I am grateful. This section is not a comprehensive list of all who have helped me along the way, but intended to recognize those whose efforts have directly made this dissertation possible.

Several Ohio State staff members deserve special recognition. Ryan Gilbert helped greatly in my orientation to the tools and supplies available for the construction and repair of the custom electronic equipment required for my project. I am grateful for the diligent computer and network maintenance provided formerly by Olaf Stein and extensively by Milan Koppen, which secured my acquired data and gave me the tools to analyze it efficiently. Similarly, I would like to thank Dr. Amir Abduljalil for administering the Linux machine that I used for image analysis. I am also greatly indebted to him for his repeated and extensive help in troubleshooting the artifacts and technical problems I encountered in image acquisition and the software errors that periodically occurred during image analysis. Consultations with Dr. Soledad Fernandez and analysis by Lai Wei in the department of Biostatistics have also enhanced the analysis of my data.
I will probably never be able to repay two particular former fellow students who taught me more practical information about FMRI than any textbook or article. I am indebted to Dr. Madalina Tivarus for her many personal training sessions in the use of FSL that made me an expert user before her graduation. Dr. Jim Ibinson has mentored me in several ways; he laid the foundation for much of my research with his own PhD dissertation and has been a consultant on all of my projects. Both Jim and Madalina worked side-by-side with me in initially getting FMRI implemented on the 3 T scanner and I thank them both for all their time and help.

It is to my committee members that I collectively owe the most gratitude for the extensive time they have contributed to my education. I would first like to thank Dr. David Clark and Dr. Douglas Gould from the division of anatomy for their engaging education on functional neuroanatomy and helpful discussions about my project. Dr. Cynthia Roberts has greatly contributed to my growth as a researcher through her critical analysis of my work and her enthusiastic attention to detail in the application of science and engineering to medical problem solving. Dr. Petra Schmalbrock has taught me many difficult to comprehend concepts about MRI fundamentals and spent a great deal of time training me on scanner operation. I very much appreciate the many discussions and meetings we have had to review results and design experiments that have shaped the data contained in this dissertation. Last, but certainly not least, I would like to acknowledge the significant commitment Dr. Robert Small made to my education. His perspective as a clinician and engineer has been very influential in the direction of this project. The many hours I have spent with him have provided a valuable glimpse into the world of academic medicine and he has made countless suggestions that have greatly improved the quality
of my work. His commitment to evidence-based medical practice has, by example, heightened my critical thinking skills. I also thank him for securing all of the financial support I have received from the department of Anesthesiology.

I am grateful for the funding provided to me by The Ohio State University. Portions of my graduate education were funded by a University Fellowship, the Medical Scientist Program, and the department of Anesthesiology. Support from the department of Radiology also funded portions of this project. Funding for payment of subjects was provided by the Alumni Grant for Graduate Research and Scholarship administered by the Graduate School.

I would like to thank all my subjects for volunteering. I am also grateful for the insight provided by critical reviews of my work from many fellow students and anonymous journal reviewers. I should also acknowledge the RETROICOR script used in chapters 3 and 4 was given to me by Jacco de Zwart of the National Institutes of Health, with permission of the original author, Gary Glover of Stanford University. Finally, I would like to thank Sara for her personal support during the various aspects of this work, and for being ever-willing to help in whatever way possible.
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CHAPTER 1

INTRODUCTION

Functional magnetic resonance imaging (FMRI) is a noninvasive tool to study brain activity. Since its inception over 15 years ago (Belliveau et al., 1991; Ogawa et al., 1992), FMRI use has become widespread while the results have become refined. The most commonly used FMRI technique depends on blood oxygen-level dependent (BOLD) contrast. As suggested by its name, BOLD contrast depends on changes in blood oxygenation that indirectly reflect neuronal activity. Specifically, there is a magnetic susceptibility difference between paramagnetic deoxyhemoglobin and diamagnetic oxyhemoglobin found in blood. BOLD imaging uses an FMRI pulse sequence that is sensitive to these microscopic susceptibility differences and generates images described as having T2* (an MR signal decay time constant) weighted contrast. The relative ratio of oxyhemoglobin to deoxyhemoglobin, reflected in the blood oxygenation level, affects the local tissue T2* time. This manifests as contrast (intensity differences) in BOLD-weighted images and quantitatively captures changes in blood oxygenation.

In FMRI, many low-resolution BOLD-sensitive images of the brain are collected over time, creating a 4-dimensional dataset. Images are acquired during an experimental task and are compared to baseline (rest) images to determine locations of differences in
brain activity. The chain of events linking neuronal activity to the BOLD response seen in the image timeseries is complex and fully reviewed elsewhere (Heeger and Ress, 2002), but an overview of the major steps is described here. Following neuronal depolarization, local increases in aerobic metabolism necessitate an increase in oxygen extraction from the cerebral capillaries. This initial effect temporarily decreases the MR signal intensity due to a decrease in the relative oxyhemoglobin to deoxyhemoglobin ratio. An autoregulatory increase in local cerebral blood flow (CBF) occurs a few seconds later. This CBF increase overcompensates for the increased metabolic demand and results in an increase in blood oxygenation compared to before the increase in neuronal activity. These oxygenation changes and reactive blood flow changes create regional differences in the BOLD signal that map the locations of underlying neuronal activity. This was validated using a motor task; BOLD FMRI signal variations were significantly correlated in space to changes in both blood flow and blood oxygen extraction fraction, measured with positron emission tomography using $\text{H}_2^{15}\text{O}$ and $^{15}\text{O}_2$ radioactive tracers (Ito et al., 2005). In dual contrast FMRI, where both BOLD and blood flow timecourses were concomitantly and independently measured, areas with significant changes in CBF during a visual task overlapped the areas with significant BOLD changes (Aguirre et al., 2002).

All MR imaging techniques are sensitive to intensity changes due to motion or any perturbation of the scanner magnetic field. Precautions are taken and post-processing employed to minimize these effects, however breathing and cardiac contraction during scanning still cause fluctuations in the images. BOLD FMRI is sensitive to any changes in either blood flow or blood oxygenation, not only those caused by neuronal activation.
Those signal fluctuations that result from quantifiable physiologic sources, termed physiologic noise, are the focus of this dissertation. The specific mechanisms by which physiologic noise contaminates the FMRI data are discussed in detail subsequently. Each of the following three chapters presents an incremental study of physiologic noise correction in functional MRI. Collectively, these studies work toward determining the optimal set of physiologic noise correction tools that may be used to improve the results of FMRI experiments.

Chapter 2 presents a novel physiologic noise correction algorithm with the descriptive name: Retrospective Slice-wise Linear Image-space Correction including ETCO₂ (RetroSLICE). This technique directly regressed measured respiratory, cardiac, and capnometry data against simultaneously acquired pain FMRI data. Intensity changes in each voxel timeseries that were significantly correlated to changes in one of these measured physiologic variables were subtracted to yield image data corrected for each type of physiologic noise. The incremental effect of each noise correction was assessed in terms of temporal noise reduction, model fit improvements, and changes in the number of activated voxels. This noise correction technique was developed at Ohio State as a preliminary method to address the problem of physiologic noise in pain FMRI data. Characterizing the effects of this in-house algorithm allowed for subsequent comparison to techniques used by other researchers.

The RetroSLICE algorithm included the use of ETCO₂ data to correct task FMRI data for the potential confound of CBF fluctuations. However, the dynamics of the BOLD response to changes in ETCO₂ were not precisely determined. Comparing two recent studies (Wise et al., 2004; Wise et al., 2007), the correlation between ETCO₂
changes and BOLD signal changes vary widely based on the function used to relate the two. In chapter 3, an optimized transfer function relating ETCO₂ changes to BOLD FMRI signal changes was developed and validated. This ETCO₂ response function was compared to a recently developed analog claimed to approximate ETCO₂ changes, the respiration response function coupled with the respiratory volume over time (RVT) measurement (Birn et al., 2008). RVT and ETCO₂ data were examined for their correlation to two FMRI datasets with different tasks: paced hyperventilation and painful stimulation.

Chapter 4 focuses on the popular respiratory and cardiac noise correction algorithm, RETROspective Image CORrection (RETROICOR), developed by other researchers (Glover et al., 2000). RETROICOR was implemented on pain FMRI data acquired at two field strengths, 1.5 and 3.0 T, and the results were quantified and compared using summary statistics, including those in chapter 2. The data calculated in chapter 4 also allowed direct comparison with the results from chapter 2 for RetroSLICE performed at 1.5 T. Two changes were made in a modified implementation of the RETROICOR algorithm: allowing a higher input sampling rate for the physiologic data and correcting for the interleaved image slice acquisition order. The impact of these modifications was assessed by comparing results from the two implementations. Finally, ETCO₂ correction was applied in addition to RETROICOR, using the optimal transfer function determined in chapter 3. The impact of ETCO₂ correction was compared to that of RETROICOR alone and was compared across the two acquisition field strengths.
CHAPTER 2

RETROSPECTIVE SLICE-WISE LINEAR IMAGE-SPACE CORRECTION
INCLUDING END-TIDAL CO$_2$ (RETROSLICE) APPLIED TO PAIN FMRI

2.1 Introduction

Functional magnetic resonance imaging (FMRI) is a well-known tool in the neurosciences that can be used to explore brain function. The repertoire of cognitive tasks being used by researchers has expanded to include areas of interest more difficult to reliably image than the primary visual and motor cortices initially demonstrated (Kwong et al., 1992). Because of the ever-increasing desire to perform high spatial resolution functional imaging of tasks that induce small FMRI signal changes, noise reduction in FMRI data has been approached from many angles. Gross image artifacts have been addressed by the use of parallel imaging (Preibisch et al., 2003). Hardware noise resulting in signal spikes or baseline drift is reduced by temporal filtering and mean intensity normalization in most FMRI analysis pipelines.

A large fraction of the noise in FMRI time-series is from physiologic sources, and this proportion increases linearly with static magnetic field strength (Kruger et al., 2001). Many strategies aimed at physiologic noise reduction have been presented. Fluctuations
in MRI signal at frequencies similar to the cardiac and respiratory cycles are prevalent throughout the brain. Filtering of the FMRI time-series to reduce the impact of these physiologic noise sources has been explored using band-reject filters (Biswal et al., 1996) and more complex filtering techniques (Deckers et al., 2006). Pre-whitening is a preprocessing step that can account for some physiologic noise by autoregressive modeling, but this has been show to inadequately model the localized effects of cardiac noise (Lund et al., 2006). Data about cardiac and respiratory fluctuations can be extracted from the FMRI data itself and used retrospectively to correct the images (Le and Hu, 1996; Chuang and Chen, 2001; Beall and Lowe, 2007; Cheng and Li, 2008). Methods have also been implemented that make use of externally acquired physiologic monitoring data applied to correct either k-space (Hu et al., 1995) or image-space (Glover et al., 2000) data. These techniques focus almost universally on respiratory and cardiac correction. However, fluctuations in end-tidal carbon dioxide (ETCO₂) are known to cause blood oxygen-level dependent (BOLD) signal changes (Wise et al., 2004). The ETCO₂ concentration approximates the arterial CO₂ concentration, which is known to affect cerebral blood flow (Grubb et al., 1974; Panerai et al., 2000). Because of this potential confound, ETCO₂ changes were explored as an additional physiologic noise regressor in this study.

Pain is a sensory task that, when experimentally delivered during functional imaging, generally causes activation throughout the cortex, cerebellum, basal ganglia, and thalamus (Coghill et al., 1999). Pain activation is commonly detected in areas at the extremes of the brain in the anterior-posterior and superior-inferior dimensions and involves both superficial and deep structures. Pain-induced FMRI signal changes are on
the order of 1 to 2.5% at 1.5 T (Becerra et al., 1999; Ibinson et al., 2004). This combination of low amplitude signal change and widespread pattern of activation makes pain FMRI acquisition difficult to optimize.

Physiologic noise correction in pain FMRI experiments is expected to be particularly important due to the potential for stimulus-induced changes in breathing and heart rates. Autonomic nervous system output is known to be modulated by pain (Akselrod et al., 1981; Stancak et al., 1996; Colloca et al., 2006). Resulting physiologic changes relevant to FMRI have been demonstrated, including stimulus-correlated increases in respiratory rate and tidal volume and decreases in ETCO$_2$ concentration, heart rate, and cerebral blood flow (Ibinson and Small, 2004). For reference, the data showing significant changes in respiratory rate, tidal volume, and ETCO$_2$ from previous work (Ibinson, 2004) is shown in Appendix A.

Because each image slice was acquired at different portions of the cardiac and respiratory cycles, physiologic noise was expected to affect each slice in an image volume differently. There is further evidence that changes in lung volume throughout the respiratory cycle cause signal changes in susceptibility-weighted images (Raj et al., 2001). Since the effect from susceptibility changes have been shown to vary with distance from the chest (Van de Moortele et al., 2002), axial slice orientation was chosen such that this respiratory noise source would have a relatively homogenous effect on each image slice. Slice-by-slice physiologic noise correction schemes based on linear regression for axially acquired whole-brain pain FMRI data using measured respiratory (Ibinson et al., 2005) and cardiac (Vogt et al., 2006) fluctuations have been demonstrated to improve model fit, eliminate false activations, and allow detection of true activations.
previously masked by physiologic noise. The use of linear regression allowed limiting the application of correction, and thus the manipulation of acquired FMRI data, to voxels where a significant correlation was detected between the physiologic and functional data time-series.

The physiologic noise correction method described here is given the descriptive name: Retrospective Slice-wise Linear Image-space Correction including ETCO₂ (RetroSLICE). As will be described in detail, this straightforward technique directly regresses collected respiratory, cardiac, and capnometry data against the FMRI timecourse at each voxel. The purpose of this study was to examine and quantify the effects of each component of this noise correction algorithm applied to a pain FMRI experiment at 1.5 T. A model-building approach was taken and the incremental effect of each noise correction technique was assessed in terms of variance reduction, model fit, and number of activated voxels. We hypothesized that each noise correction technique would have additive improvements in each of these measured parameters by reducing variance, increasing the measure of model fit, and increasing the number of activated voxels.

2.2 Methods

In this study, three types of physiologic monitoring were performed on subjects during a pain FMRI experiment. Linear regression of the physiologic data against the FMRI data allowed for noise correction in voxels significantly contaminated with instantaneous signal changes correlated to variations in one or more physiologic parameters. In this chapter, physiologic noise is operationally defined as fluctuations in
the acquired FMRI data that can be attributed to variations in acquired physiologic measurements. The overall steps taken in image and physiologic data processing and analysis are shown in Fig. 2.1.

Eight healthy, right-handed adult subjects were recruited in this study approved by The Ohio State University Institutional Review Board. Informed consent was obtained from all subjects and they were free to withdraw at any time. For subject 4, the functional scan showed head motion > 2 mm and was excluded from further analysis. The remaining seven subjects whose data is presented here had the following gender and age distribution: 4 male, 3 female, mean age 31.1 ± 6.8 years (standard deviation), age range 26 – 46 years.

Transcutaneous electrical nerve stimulation was used as the painful stimulus. Two electrodes were placed on the lateral aspect of the right index finger, straddling the proximal interphalangeal joint. This location was selected to stimulate the digital nerve in the finger and avoided the muscle contractions that accompany stimulation of more proximal nerves. An intra-operative nerve stimulator (Life Tech, MaxiStim Model ST6, Stafford, TX) was connected to the electrodes. A 100 Hz sinusoidal waveform was used for painful stimulation.

To determine the appropriate intensity for each subject, a familiarization session was performed prior to the imaging session and outside the MRI environment. Following electrode application, stimulator intensity was gradually increased while the subjects continuously rated the intensity of the pain sensation verbally on a 0 to 10 scale, where 0 was no pain and 10 was the worst pain imaginable. The stimulator intensity was
increased until the subject reported a verbal pain scale rating of 5 out of 10. This same current level was then used for the painful stimulation during FMRI scanning.

The experiment consisted of four 30-second periods of painful stimulation interleaved with 30-second rest periods during which no stimulation was delivered. For the first four subjects, 30 seconds of initial rest preceded the first painful stimulation, giving a total experiment time of 4.5 minutes. In order to better characterize the physiologic baseline before painful stimulation, this initial rest period was increased to 60 seconds for subjects 5 through 8, making the experiment 5 minutes long.

All imaging was performed with a 1.5 T General Electric Medical (Milwaukee, WI) Signa scanner (Revision 8.4). A high-resolution three-dimensional T1-weighted anatomical brain image for mapping each subject’s FMRI images was obtained using the following parameters: TR = 20 s, flip angle = 40º, 256x128 matrix, FOV = 24 cm, slice thickness = 2.5 mm, 60 axial slices. The functional scans were collected with a BOLD sensitive single-shot gradient echo, echo-planar imaging technique using a transmit-receive head coil and the EPIBOLD software (General Electric Medical) with the following parameters: TR = 3 s, TE = 50 ms, flip angle = 90º, 64 x 64 matrix, FOV = 24 cm, in-plane resolution = 3.75 x 3.75 mm, and slice thickness = 5 mm. The phase-encode direction was anterior-posterior. Twenty-eight (28) axial slices with no gap were acquired in an interleaved fashion giving whole brain coverage. The first five volumes from each scan were discarded since the MR signal had not yet reached steady-state. The acquired functional datasets consisted of either 95 or 105 volumes (time points) based on the length of the initial rest period. Thus, the total functional scan time was 4 min 45 sec for the first four subjects and 5 min 15 sec for the last four subjects. Raw images were
reconstructed offline using the EPIRECON software (General Electric Medi cal). During reconstruction, a Fermi filter with a width of 10 mm and radius of 32 mm was used to avoid truncation artifacts.

Respiratory, cardiac, and capnometry monitoring were performed throughout the FMRI experiment. A respiratory belt (RB) strain gauge was placed around the chest near the inferior costal margin. This sensor gave a voltage signal directly proportional to changes in chest circumference that occurred with breathing. A pulse plethysmograph (PPG) sensor was placed on one of the subject’s fingers to measure the changes in peripheral blood that occur with each heartbeat. This sensor gave a plot of each cardiac cycle, reflected by the peripheral pulse waveform. Finally, expired air was sampled with a nasal cannula connected to a Datex Capnomac Ultima clinical gas monitor (GE Healthcare Bio-Sciences Corp., Piscataway, NJ). This monitor had an analog voltage output that was a scaled version of the expired CO₂ concentration waveform. Subjects were instructed to breathe through their nose for the sake of this sampling method.

The analog output of each of these sensors was connected to three individual input channels on a BIOPAC MP-30 data acquisition unit (BIOPAC Systems Inc., Sacramento, CA). The fourth input channel on the BIOPAC was used to capture a trigger signal from the scanner given each time a slice was acquired. These inputs were digitally sampled at 200 Hz and the resulting data was stored on an attached computer using BIOPAC Student Lab Pro software version 3.7.0 (BIOPAC Systems). The time scales for all four acquisition channels were synchronized, so the value of each physiologic parameter at the time of each slice acquisition could be determined.
Temporal filtering of the physiologic data was performed with AcqKnowledge version 3.5.7 (BIOPAC Systems). The RB and PPG data were both low-pass filtered using a digital infinite impulse response filter with a cutoff of 2 Hz to remove high frequency signal fluctuations caused by interference from the rapid switching of the gradient magnets. At this point, the physiologic waveforms were visually inspected for gross signal artifacts. The three physiologic waveforms were resampled using AcqKnowledge at the time of each slice acquisition, as indicated by the trigger signal from the scanner. Further processing of the RB and PPG waveforms to determine slice-wise noise regressors was done using the code shown in Appendix B written in MATLAB (The Math Works, Natick, MA). Both RB and PPG data were reordered to account for the interleaved slice acquisition order. The resampled and reordered RB amplitude data was used to create the slice-wise respiratory noise regressor, $X_{RB}$, shown in Fig. 2.1. The PPG timecourse was analyzed to determine the peak timing for each heartbeat. The phase of the cardiac cycle during each image slice acquisition was calculated, as in the work by Dagli et al. (1999). This operation assigns a unit cycle value between 0 and 1 to the PPG noise regressor, $X_{PPG}$, based on the timing of each slice acquisition in the peak to peak cardiac cycle. Amplitude variations in the PPG timecourse were not used in the noise correction analysis.

The expired CO$_2$ waveform was time-shifted by 17 s to account for the time delay for the expired air to traverse the sampling tubing and reach the gas monitor. This time-shifted waveform was processed in AcqKnowledge to determine the peak value at the end of expiration, which is equal to the ETCO$_2$ value. In this way, one ETCO$_2$ value per breath was extracted from the expired CO$_2$ waveform. To create the volume-wise ETCO$_2$
noise regressor, $X_{CO2}$, the corresponding ETCO$_2$ value was assigned to each acquisition volume (TR interval). If no breath occurred in a TR interval, the last known ETCO$_2$ value was used as the regressor for that volume. Since a typical breath and its corresponding ETCO$_2$ value was separated by 3 to 5 seconds, applying ETCO$_2$ correction on a slice-wise basis proved to be unnecessary.

The functional images were preprocessed using FMRIB’s Software Library (FSL) version 3.2. This consisted of motion correction (Jenkinson et al., 2002), brain extraction (Smith, 2002), and spatial smoothing using a Gaussian kernel with a full-width half maximum of 5 mm. High-pass temporal filtering using a Gaussian-weighted least squares straight line fit with sigma = 45 seconds was performed to remove baseline signal fluctuations. Slice-timing correction for the interleaved acquisition order was applied using Fourier-space time-series phase-shifting. These transformations created the preprocessed image data set, designated as $Y_0$ in Fig. 2.1, which was used for further analysis, including physiologic noise removal. By design, smoothing, motion correction, and temporal filtering reduce the variance in the FMRI data. In light of this, applying physiologic noise correction after the preprocessing step in the data analysis pipeline should allow the most accurate quantification of the effects of physiologic noise correction on FMRI data analysis, as the regression was performed against the data with standard non-physiologic denoising already applied.

Respiratory and cardiac noise correction was accomplished by performing slice-wise linear regression of the calculated physiologic noise regressors against each voxel timecourse in the preprocessed FMRI data using MATLAB. Physiologic noise contamination was considered present in each voxel with a significant ($p < 0.05$)
regression coefficient. Noise was removed from the FMRI data in contaminated voxels by subtracting the portion of signal in that voxel that was correlated to the physiologic noise regressor. ETCO$_2$ correction was performed as a part of the general linear model (GLM) used to determine brain activation due to pain. The RetroSLICE algorithm was performed in a step-wise manner, as shown in Fig. 2.1. To analyze the contributions of each type of noise correction, each was also applied to the data individually and in every possible combination of two parameters by executing the corresponding portions of the correction algorithm shown in Fig. 2.1.

Functional activation maps were determined by general linear modeling of the uncorrected data and of datasets with physiologic noise correction applied using FEAT version 5.4 (Woolrich et al., 2001). All maps shown were calculated for positive BOLD changes with a one-tailed test. When included, ETCO$_2$ correction was applied as a second explanatory variable in the GLM, with one value per volume. Both the square-wave function representing the pain stimulus timing and the ETCO$_2$ timecourse were convolved with the default hemodynamic response function, which had a time to peak of 6 s. This accounts for the delay for the hemodynamic response to neural activity and the delay between ETCO$_2$ changes (already time-shifted to account for the sampling delay) and the resulting changes in the BOLD images, both of which have been shown to be approximately 6 seconds (Aguirre et al., 1998; Wise et al., 2004). Optimization of the response function used for ETCO$_2$ convolution is the focus of chapter 3.

Individual subject Z-score maps were generated and thresholded to only display clusters with $Z > 2.3$ and a multiple comparison corrected significance of $p < 0.05$ (Worsley et al., 1992). Registration to high resolution and/or standard images was
carried out using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002). All image registrations were visually inspected to ensure a good match between the source and target images. Individual subject statistical parameter maps were co-registered to the Montreal Neurological Institute (MNI) standard space template, which allowed averaging across subjects. Group analysis was performed with FLAME (Beckmann et al., 2003; Woolrich et al., 2004b) and maps were thresholded using clusters with $Z > 2.0$ and a cluster significance threshold of $p < 0.05$, corrected for multiple comparisons.

The number of activated voxels in the thresholded statistical maps was calculated for each subject and each combination of noise correction. Similarly, the temporal standard deviation, $\sigma$, before and after cardiac and respiratory noise correction was calculated for each dataset. Since ETCO$_2$ correction was applied as part of the GLM, the FMRI data was not modified and no change in $\sigma$ was seen with the addition of ETCO$_2$ to a given model.

The residuals from model-fitting were analyzed to determine the goodness of fit of the model used to detect brain activation due to pain. Specifically, the adjusted coefficient of multiple determination ($R^2_a$) was calculated for each voxel, as in the work by Razavi et al. (2003). This summary statistic is adjusted for the number of parameters used in the model, such that the term will decrease with the addition of an explanatory variable that does not explain its share of the variance in the data being modeled. To examine the global differences between models, the maximum and mean $R^2_a$ value across all voxels in the brain were determined for each model.
2.3 Results

The spatial effects of each type of noise correction are shown for a typical subject in Fig. 2.2. For all subjects, each of the three physiologic noise regressors had a different spatial pattern of voxels where a significant correlation was found between the physiologic monitoring and FMRI data. The effects of PPG correction were localized to areas of high vascularity, such as the circle of Willis and vertebrobasilar artery system. Respiratory corrected voxels were found more diffusely throughout the brain, with increased prevalence near the periphery. End-tidal CO₂ correction also occurred throughout the brain with a notable localization to the area of susceptibility-induced signal dropout in the inferior frontal lobes. The spatial locations of all three types of correction are displayed together in the “All” column of Fig. 2.2. This combined map shows that the correction for each noise regressor has both independent and overlapping spatial extent with the others.

The calculated across-subject average values used to quantify the effect of physiologic noise correction are listed in Table 2.1. Each row lists a model applied to the data comprised of different individual model components in the RetroSLICE algorithm. Table 2.2 lists, for comparisons of interest, the changes in the summary statistics in Table 2.1. Since ETCO₂ correction was applied as part of the GLM, the FMRI data was not modified and no change in σ was seen with the addition of ETCO₂ to a given model. The average timecourse standard deviation decreased by 4.06% with respiratory correction, while PPG correction only reduced this measure by 1.27%. The two corrections together have a slightly synergistic effect on σ, with “[RB + PPG] vs. none” showing a 5.41% decrease.
Improvements in model fit were seen with each noise correction model used. The increases seen in the maximum and mean $R^2_a$ across all subject’s data are listed in Table 2.2. Unlike $\sigma$, this summary statistic can be used to assess the effect of ETCO$_2$ correction. Including ETCO$_2$ as model parameter caused a 68.36% increase in the average $R^2_a$ value, compared to modeling only the pain stimulus. This increase was greater than the 49.27% and 16.1% increases in average model fit with respiratory and cardiac correction, respectively. Furthermore, comparing the full model (including all three corrections) to that with respiratory and cardiac correction, as with “Full Model vs. [RB + PPG]” in Table 2.2, shows a 38.87% increase in average model fit with the addition of ETCO$_2$ correction. Overall, the full RetroSLICE algorithm, including RB, PPG, and ETCO$_2$ noise corrections, resulted in a 129.1% increase in $R^2_a$. This indicates a substantial improvement in GLM fit to the pain FMRI data acquired in this study by including all three available physiologic variables.

The average number of activated voxels in the pain activation map calculated with each model are listed in the final column of Table 2.1. Each correction caused both gains and losses of activated voxels in both individual subject and group average activation maps. Only the whole-brain net change in the number of activated voxels is reported in Table 2.1. Changes in this average net change in voxel count when different combinations of noise regressors were included in the model are listed in Table 2.2. Generally, ETCO$_2$ correction tended to increase the number of overall activated voxels, while respiratory and cardiac correction caused decreases in voxel count. When the full model was applied and all three noise corrections interacted, the change in the average number of activated voxels was reduced by less than 1%.
Fig. 2.3 shows selected slices of the group average pain activation maps without (top row) and with (bottom row) physiologic noise correction overlaid on the MNI standard brain. In this figure, slices were selected to display the diffuse activation throughout the brain in response to pain. Areas detected as activated in this study are consistent with those reported in reviews of pain functional imaging studies (Peyron et al., 2000; Apkarian et al., 2005). For right hand painful electric nerve stimulation, robust activation was detected both before and after physiologic noise correction in the left cerebellum, right basal ganglia, bilateral insula, left prefrontal cortex, and in the primary and secondary somatosensory cortices bilaterally.

Differences between the uncorrected and corrected pain activation maps were caused by one or more noise correction steps, as indicated by the color map displayed in the middle row of Fig. 2.3. In the seven slices shown, examples of both gains and losses in activated voxels are demonstrated for each type of physiologic noise correction as shown by the voxels shaded yellow, blue, and red. Examples of activation map changes due to more than one model parameter are also seen, indicated by the voxels shown in green, orange, purple, and white. The large number of voxels in which group average activation was detected irrespective of noise correction are shaded gray in the middle row of Fig. 2.3.

The most striking change in the group activation maps with physiologic correction are seen in the three slices displaying the thalamus, shown in Fig. 2.4. Bilateral thalamic activation in the uncorrected map was entirely removed by the inclusion of ETCO2 correction. Because of this unexpected activation map change, the difference in mean $R^2_a$ with ETCO2 correction was calculated by averaging specifically
in a thalamic region of interest (ROI). The inclusion of ETCO₂ data into the GLM improved average model fit in the thalamus by 79.72%, which was greater than the 68.36% increase seen in mean \( R^2 \) seen across the whole brain (Table 2.2, “ETCO₂ vs. none”).

### 2.4 Discussion

The RetroSLICE technique presented in this chapter is similar to RETROICOR (Glover et al., 2000) in that it is a retrospectively applied image-space correction that uses physiologic data obtained from patient monitoring. RetroSLICE differs from the well-established FMRI noise correction technique, RETROICROR, in two ways: the assumption of an instantaneous effect of physiologic fluctuations on the BOLD signal and the inclusion of ETCO₂ correction. The slice-wise regression of the respiratory and cardiac variables performed in RetroSLICE determined the correlation between physiologic data acquired during the entire experiment and the individual image voxel timeseries. RetroSLICE only corrected the data at voxels where the correlation passes a significance threshold of \( p < 0.05 \). This method was thus unlikely to induce more correlation between voxels and should not add noise to the data. RetroSLICE does not include the sinusoidal fitting procedure performed in RETROICOR. Rather, it applied individual physiologic data points acquired during imaging were to the FMRI data at the point in the time-series corresponding to when they were acquired. In this way, instantaneous values for physiologic parameters were applied to the data, with no spectral limits on frequency. No analysis of the impact of respiratory and cardiac noise correction has been previously
reported for a pain FMRI experiment. A comparison between the performance of RetroSLICE and RETROICOR is performed in Chapter 4.

RetroSLICE also includes ETCO₂ values as a noise regressor. In the seminal work by Wise et al. (2004), ETCO₂ fluctuations at rest were shown to be correlated to BOLD signal changes throughout the brain. By means of equilibrium maintained by gas diffusion, the CO₂ concentration in expired air at the end of expiration should approximate the alveolar CO₂ concentration, which is equal to the concentration of CO₂ in the pulmonary circulation. By this chain of equivalence, the ETCO₂ concentration can be used to estimate the systemic arterial CO₂ concentration. Because of vasodilatory effects of CO₂ in blood, changes in arterial CO₂ concentration have a linear effect on global cerebral blood flow (CBF) (Grubb et al., 1974). The painful electric nerve stimulation paradigm used in this study caused significant increases in respiratory rate and tidal volume and a corresponding decrease in ETCO₂ over the course of the experiment (Ibinson and Small, 2004). This ETCO₂ decrease is expected to cause a decrease in CBF, which would decrease the baseline BOLD signal (Liu et al., 2007). A BOLD signal change such as this, which is not related to the functional task, would confound the determination of brain activation by causing a signal change in brain volumes acquired later in the experiment. Correction for changes in respiratory rate and tidal volume over the course of an experiment, indirectly correcting for ETCO₂ changes, has been recently demonstrated to improve identification of task-related activation (Birn et al., 2006). The demonstration in this chapter of ETCO₂ correction applied to a pain FMRI experiment shows an improvement in model fit, in addition to respiratory and
cardiac noise correction, and also illustrates how task-correlated fluctuations in CBF can affect the calculated group activation map.

The spatial location of voxels suffering each type of noise contamination was consistent with distributions described in the literature. The effects of PPG correction predominated in inferior slices and were localized to areas of high vascularity, such as the circle of Willis and vertebrobasilar artery system, which is consistent with previous results (Dagli et al., 1999; Beall and Lowe, 2007; Perlberg et al., 2007). It was possible that the spatial effects of ETCO$_2$ correction would overlap with or be a subset of the respiratory correction. Figure 2.2 shows that the respiratory and ETCO$_2$ corrections had large areas where they individually had an effect, indicated by the voxels shaded blue and yellow in the column labelled “All”. Respiratory-corrected voxels were found diffusely throughout the brain with increased prevalence near the periphery and in gray matter and cerebrospinal fluid, consistent with previous reports (Windischberger et al., 2002; Birn et al., 2006; Beall and Lowe, 2007; Perlberg et al., 2007) and with theoretical predictions of respiration-induced susceptibility changes (Raj et al., 2000). End-tidal CO$_2$ changes were correlated to FMRI signal changes in many areas throughout the brain, as described by Wise, et al. (2004).

Razavi et al. (2003) first presented using $R^2_a$, the adjusted coefficient of multiple determination, as a measure of FMRI model quality. This summary statistic can be calculated for model-fitting at each voxel and has a maximum value of 1.0. In contrast to the unadjusted coefficient, $R^2$, $R^2_a$ values can decrease when additional parameters are added into the model and $R^2_a$ values can also be negative. It was initially shown for a visual task that the inclusion of cardiac and respiratory parameters in the model resulted
in GLM fit improvements indicated by $R^2_a$ increases (Razavi et al., 2003). This study replicated those results for a pain task, showing an approximately 65% increase in mean $R^2_a$ from combined RB and PPG correction. In fact, each physiologic parameter caused global model fit improvements, as shown by the consistent increases in $R^2_a$ for each case listed in Table 2.1. Overall, the full RetroSLICE algorithm, including RB, PPG, and ETCO$_2$ noise corrections, resulted in a 129% increase in average $R^2_a$ across all subjects. This indicates a substantial improvement in GLM fit to the pain FMRI data acquired in this study by including all available physiologic data. These model-fit improvements overshadowed the small overall changes in the number of activated voxels in the brain.

This chapter also showed the effects of physiologic noise correction on the group-average pain FMRI activation maps. Nearly every cluster of activation detected in the brain was affected by one or more type of physiologic noise correction. The most noticeable change occurred with the bilateral thalamic activation seen in the uncorrected map, as shown in Fig. 2.4. The elimination of thalamic activation was almost exclusively caused by ETCO$_2$ correction. This is contrary to the results of Wise et al. (2004), which did not show a statistically significant correlation between ETCO$_2$ fluctuations and BOLD signal changes in the thalamus. However, pain-induced ETCO$_2$ changes can be significantly larger (Ibinson and Small, 2004) than the resting fluctuations studied by Wise et al. (2004). As such, the ETCO$_2$ timecourse in this experiment was likely significantly correlated to FMRI signal changes in deeper brain areas.

A lack of thalamic activity in the group average maps for an FMRI experiment studying pain processing is incongruent with the known neuroanatomical synapse of ascending spinothalamic tract neurons in the thalamus. Nonetheless, the thalamus has
been inconsistently reported as activated in FMRI studies of pain (Peyron et al., 2000; Apkarian et al., 2005). This reflects the difficulty in reliably detecting activation in the deep brain structures using FMRI. The thalamus is also located in a highly-vascularized area of the brain such that changes in blood flow correlated to changes in ETCO₂ may lead to BOLD signal fluctuations resulting in activation. The localized thalamic ROI improvement in $R^2_a$ with ETCO₂ correction seen concomitantly with the loss of thalamic activation indicates an improvement in model fit, despite the reduction in activated voxels.

### 2.5 Conclusions

This chapter presents a novel physiologic noise correction algorithm for FMRI, RetroSLICE, which assumes an instantaneous noise contamination effect in FMRI data from changes in respiratory, cardiac, and ETCO₂ monitoring. Application of this technique improved the ability to determine brain activation in a pain FMRI experiment. The improvements in model fit with the inclusion of ETCO₂ correction exceeded those from combined cardiac and respiratory correction and had noticeable effects on the average group activation maps. These results illustrate the impact of including ETCO₂ correction in the analysis of pain FMRI data and suggest the need for expanded FMRI physiologic noise correction algorithms in addition to those currently in use.
2.6 Tables and figures

<table>
<thead>
<tr>
<th>Model</th>
<th>σ</th>
<th>Max $R^2_a$</th>
<th>Mean $R^2_a$</th>
<th>Voxel Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Only</td>
<td>36.37 ± 6.95</td>
<td>0.3856 ± 0.0687</td>
<td>0.0354 ± 0.005</td>
<td>393.0 ± 215.7</td>
</tr>
<tr>
<td>Pain + RB</td>
<td>34.90 ± 7.16</td>
<td>0.5718 ± 0.1201</td>
<td>0.0528 ± 0.008</td>
<td>354.4 ± 123.9</td>
</tr>
<tr>
<td>Pain + PPG</td>
<td>35.91 ± 6.88</td>
<td>0.4360 ± 0.0700</td>
<td>0.0411 ± 0.006</td>
<td>380.4 ± 196.0</td>
</tr>
<tr>
<td>Pain + ETCO₂</td>
<td>36.37 ± 6.95</td>
<td>0.4391 ± 0.0748</td>
<td>0.0596 ± 0.016</td>
<td>427.4 ± 433.7</td>
</tr>
<tr>
<td>Pain + RB + PPG</td>
<td>34.41 ± 7.09</td>
<td>0.6057 ± 0.1084</td>
<td>0.0584 ± 0.014</td>
<td>319.7 ± 335.3</td>
</tr>
<tr>
<td>Pain + RB + ETCO₂</td>
<td>34.90 ± 7.16</td>
<td>0.5989 ± 0.1080</td>
<td>0.0755 ± 0.008</td>
<td>408.1 ± 148.8</td>
</tr>
<tr>
<td>Pain + PPG + ETCO₂</td>
<td>35.91 ± 6.88</td>
<td>0.4539 ± 0.0773</td>
<td>0.0653 ± 0.017</td>
<td>417.3 ± 415.2</td>
</tr>
<tr>
<td>Pain + RB + PPG + ETCO₂</td>
<td>34.41 ± 7.09</td>
<td>0.6250 ± 0.1104</td>
<td>0.0811 ± 0.016</td>
<td>389.9 ± 321.3</td>
</tr>
</tbody>
</table>

Table 2.1. Whole brain, across subject averages of standard deviation, adjusted coefficient of multiple determination, and activated voxel counts for each model used. Values listed are mean ± standard deviation across subjects. $\sigma$ represents the temporal standard deviation of the preprocessed FMRI data timecourse.

<table>
<thead>
<tr>
<th>Correction Comparison</th>
<th>$\Delta\sigma$</th>
<th>$\Delta\text{Max } R^2_a$</th>
<th>$\Delta\text{Mean } R^2_a$</th>
<th>$\Delta\text{Voxel Count}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB vs. none</td>
<td>-1.48 (-4.06)</td>
<td>0.1362 (48.28)</td>
<td>0.0174 (49.27)</td>
<td>-38.6 (-9.81)</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-0.46 (-1.27)</td>
<td>0.0504 (13.06)</td>
<td>0.0057 (16.10)</td>
<td>-12.6 (-3.20)</td>
</tr>
<tr>
<td>ETCO₂ vs. none</td>
<td>-</td>
<td>0.0535 (13.87)</td>
<td>0.0242 (68.36)</td>
<td>34.4 (8.76)</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-1.97 (-5.41)</td>
<td>0.2201 (57.08)</td>
<td>0.0230 (64.97)</td>
<td>-73.3 (-18.65)</td>
</tr>
<tr>
<td>[RB + ETCO₂] vs. RB</td>
<td>-</td>
<td>0.0271 (4.75)</td>
<td>0.0227 (42.88)</td>
<td>53.7 (15.16)</td>
</tr>
<tr>
<td>Full model vs. [RB + PPG]</td>
<td>-</td>
<td>0.0193 (3.19)</td>
<td>0.0227 (38.87)</td>
<td>70.1 (21.94)</td>
</tr>
<tr>
<td>Full model vs. none</td>
<td>-1.97 (-5.41)</td>
<td>0.2394 (62.09)</td>
<td>0.0457 (129.10)</td>
<td>-3.1 (-0.80)</td>
</tr>
</tbody>
</table>

Table 2.2. Comparisons between models listed in Table 2.1. Values listed are difference (% change). Pain is included in all models listed. Full model refers to the Pain + RB + PPG + ETCO₂ model listed in the last row of Table 2.1. Since ETCO₂ correction was applied as part of the GLM, the FMRI data was not modified and the time course standard deviation, $\sigma$, did not change.
Figure 2.1. Flow chart showing the multiple regression steps used to remove respiratory (RB), cardiac (PPG), and capnometry (CO2) variations from the FMRI data. For each step, the equation for the general linear model $Y_n = B_nX_n + C_n + e_n$ is used in which $Y_n$ is the 4-D data, $B_n$ is the 3-D coefficient of regression matrix, $X_n$ is the 1-D (time) model of the regressor, and $C_n$ and $e_n$ are the 4-D matrices containing the constants and residuals for each voxel at each point in time. RC = respiratory correction, PC = PPG correction.
Figure 2.2. Series of brain images showing the spatial effects of each physiologic noise correction on selected slices from a single subject. The first two columns, labelled RB and PPG, show the regression coefficient matrix from, respectively, respiratory and cardiac noise correction thresholded for voxels in which a significant correlation existed between the FMRI and physiologic data. The column labelled CO₂ shows the Z-score map of significant ETCO₂ noise as calculated from the GLM. The final column, labelled All, is a concatenated map of the spatial location of each type of noise throughout the slice. Each type of correction is represented by a primary color and voxels affected by more than one type are colored a combination of these, according the key shown. The combined map does not display intensity information.
Figure 2.3. Group average pain activation maps, overlaid on the MNI standard brain, with slices selected to show the diffuse activation in response to pain throughout the brain. Activation maps are shown both without physiologic noise correction (top row) and with all three noise corrections applied (bottom row). The middle row shows, by the color system on the right, which type(s) of physiologic noise correction were responsible for changes in the activation state of a voxel.
Figure 2.4. Group average pain activation maps, overlaid on the MNI standard brain, with slices showing the change in thalamic activation between the uncorrected (top row) and corrected (bottom row) maps. The middle row shows, by the color system on the right, which type(s) of physiologic noise correction were responsible for changes in the activation state of voxel.
CHAPTER 3

CAPNOMETRY CORRECTION IN FUNCTIONAL MRI: THE END-TIDAL CO₂ RESPONSE FUNCTION

3.1 Introduction

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (FMRI) is widely used to map neuronal activity in the brain based on localized fluctuations in blood oxygenation (Ogawa et al., 1990). The cause of these changes has been explored and, though no consensus has been reached, the resulting BOLD signal changes likely involve some combination of increases in blood flow and venous volume (Buxton et al., 1998).

The arterial carbon dioxide (CO₂) concentration is known to affect cerebral blood flow (CBF) and volume (Grubb et al., 1974) due to the direct vasodilatory effects of carbon dioxide on cerebral vasculature (Brian, 1998). In healthy subjects, circulatory CO₂ readily equilibrates with the air in the lungs, which has two important implications. The first is that indirect control of arterial CO₂ can be achieved by changing the alveolar CO₂ concentration through modulated ventilation or CO₂-enriched breathing. Secondly, a measure of arterial CO₂ can be obtained from exhaled air at end-expiration, called the end-tidal CO₂ (ETCO₂) value. The ETCO₂ value is correlated to arterial CO₂ with normoventilation at rest (Robbins et al., 1990; Barton and Wang, 1994).
Experimentally increasing the inhaled CO₂ concentration has been shown to increase the baseline BOLD signal and decrease the BOLD signal change in response to functional tasks performed under hypercapnia (Bandettini and Wong, 1997; Hoge et al., 1999; Cohen et al., 2002; Stefanovic et al., 2006; Liu et al., 2007). Similarly, hypercapnia induced by breath holding and hypoventilation has been shown to increase the BOLD signal (Kastrup et al., 1998; Kastrup et al., 1999; Thomason et al., 2007) and can alter the hemodynamic response to stimulation (Vazquez et al., 2006). Conversely, hypocapnia due to hyperventilation causes decreases in the BOLD signal (Posse et al., 1997) and may also affect functional task activation (Hsu et al., 1998; Terekhin and Forster, 2006).

In healthy resting subjects, fluctuations of ± 5% in ETCO₂ occur and are correlated to fluctuations in middle cerebral artery (MCA) blood flow velocity, with a delay of 4-6 s (Panerai et al., 2000; Wise et al., 2004). These natural variations in measured ETCO₂ are also correlated to BOLD signal changes in the brain at rest (Wise et al., 2004). Widespread changes in the BOLD signal in the brain parenchyma following an experimental hypercapnic stimulus have been demonstrated, with a time delay of 12-15 s (van der Zande et al., 2005; Wise et al., 2007). These results suggest that measuring expired CO₂ concentration and correcting FMRI images for ETCO₂-correlated fluctuations could be an important addition to the commonly performed corrections for cyclic respiratory and cardiac noise, such as with RETROICOR (Glover et al., 2000).

However, because CO₂ sampling is not included as a component of MR scanner hardware, collecting this data is technically challenging. A simpler alternative measure of respiratory volume over time (RVT) has been suggested (Birn et al., 2006). The RVT
is derived from the respiratory motion tracing and presumably models arterial CO₂ changes (Birn et al., 2008). Correction for RVT changes over the course of a FMRI experiment can improve identification of task-related activation after standard noise correction with RETROICOR (Birn et al., 2006). A respiration response function (RRF) model relating RVT changes to BOLD signal changes was recently determined and (convolved with the RVT timecourse) explained BOLD signal changes from several respiratory paradigms: breath holding, breathing rate and depth changes, and quiet breathing (Birn et al., 2008). However, concordance between RVT and ETCO₂ changes has not been demonstrated, nor have these two measures been compared for their correlation to BOLD signal changes under different FMRI task conditions.

In this present study, an optimized method to correct for ETCO₂ changes in BOLD FMRI is developed and validated. A reasonable transfer function between induced ETCO₂ variations and BOLD signal changes is determined under several conditions of hyperventilation during which concomitant FMRI and expired CO₂ data were acquired. RVT and ETCO₂ data collected during scanning were convolved with their optimized transfer functions and applied to two separate task datasets: paced breathing modulation (hyperventilation) and painful stimulation. The correlation with measured BOLD signal changes were compared for RVT and ETCO₂. It was hypothesized that both RVT and ETCO₂ would adequately model BOLD signal changes in the pain FMRI dataset. However, the breathing modulation experiment was designed to effectively uncouple respiration from its normal CO₂-linked feedback control mechanism, creating a disparity between respiratory minute volume (and thus RVT)
changes and the arterial CO$_2$ level. It was thus hypothesized that ETCO$_2$ data would be more strongly correlated to BOLD fluctuations in the breathing modulation FMRI data.

### 3.2 Methods

Two 3 T BOLD FMRI datasets with different functional tasks were analyzed in this study. In the breathing modulation experiment, subjects performed a series of paced hyperventilation tasks over 10.5 minutes of scanning. This dataset was used to empirically determine the average optimal ETCO$_2$ response function, as described below. The ETCO$_2$ response function was then applied to a separately acquired pain FMRI dataset using a previously described stimulus paradigm (Ibinson et al., 2004).

Nine healthy adult subjects participated in the breathing modulation study, which was approved by The Ohio State University Biomedical Sciences Institutional Review Board (protocol number 2008H0155). The functional scan consisted of 210 acquisition volumes and was 10.5 minutes in length. The pace and depth of breathing were controlled throughout the experiment using graphical cues presented on an MR-compatible display system. All subjects had previously undergone a training session with the same graphical cues prior to entering the scanner, and all were comfortable performing the required breathing tasks. The scan consisted of nine experimental periods, as listed in Table 3.1, over which the cued respiratory rate and depth were independently varied.

Nine right-handed healthy adult subjects were recruited in the pain study, which was approved by The Ohio State University Biomedical Sciences Institutional Review Board (protocol number 2006H0069). Some, but not all, subjects participated in both
studies. Each subject underwent two scanning sessions with an identical 4.5 minute pain stimulation paradigm while 90 volumes of FMRI data were acquired. Four 30 s pain periods were interleaved with five 30 s rest periods. Transcutaneous electrical nerve stimulation was delivered via two electrodes placed on the lateral aspect of the right index finger, straddling the proximal interphalangeal joint. This location was selected to stimulate the digital nerve in the finger while avoiding the muscle contractions that accompany stimulation of more proximal nerves. An intra-operative nerve stimulator (Life Tech, MaxiStim Model ST6, Stafford, TX) was connected to the electrodes and delivered a 100 Hz sinusoidal waveform during stimulation. Following electrode application, the stimulus intensity was determined for each subject just prior to the imaging session. Nerve stimulator intensity was gradually increased while the subjects continuously rated the intensity of the pain sensation verbally on a 0 to 10 scale, where 0 is no pain and 10 is the worst pain imaginable. The stimulator intensity was increased until the subject reported a verbal pain scale rating of 5 out of 10. This same current level was then used for all painful stimulations during FMRI scanning.

Most imaging parameters were common to the acquisition of both datasets. BOLD-weighted data was acquired with a Philips 3 T Intera scanner (Philips Medical Systems, The Netherlands) using a gradient echo sequence with echo-planar-imaging readout. Whole brain coverage was achieved with 35 contiguous axial slices acquired in an interleaved fashion. The in-plane image matrix size was 64 x 64, with a final acquired voxel dimension of 3.75 x 3.75 x 4 mm. Repeat time (temporal resolution, TR) was 3 s, echo time was 30 ms, the flip angle of excitation was 90°, and the phase encode (foldover) direction was oriented along the anterior-posterior dimension. An 8-channel
head-only receive coil was used with sensitivity encoding (reduction factor 2), in an
effort to reduce the echo train length and minimize image distortion (de Zwart et al.,
2002; Preibisch et al., 2003). Four dummy scan volumes were acquired and discarded
prior to the acquisition of data used for analysis, allowing the system to reach steady-
state. Image reconstruction was performed automatically on the scanner console.

Physiologic monitoring data from each subject was recorded throughout both
FMRI experiments using the same techniques. A respiratory belt (RB) strain gauge was
placed around the subject near the inferior costal margin. This sensor gave a voltage
signal directly proportional to changes in thoracoabdominal circumference that occurred
with breathing. A pulse plethysmograph (PPG) sensor was placed on one of the subject’s
fingers to measure the oxygenation changes in peripheral blood that occur with each
heartbeat. This sensor gave a plot of each cardiac cycle, reflected by the peripheral pulse
waveform. Each subject wore a MAC-line (Oridion, Jerusalem, Israel) that allowed
simultaneous sampling of air expired through either the mouth or nose. The MAC-line
was connected by 9 m of sampling tubing to a Datex Capnomac Ultima clinical gas
monitor (GE Healthcare Bio-Sciences, Piscataway, NJ) located just outside the magnet
room. The Datex monitor continuously sampled the subject’s MAC-line at 200 mL/min
and gave an analog voltage output that was a scaled version of the expired CO₂
concentration waveform, allowing recording of the capnograph.

The analog output of each of these sensors was connected to three individual
input channels on a BIOPAC MP-30 data acquisition unit (BIOPAC Systems,
Sacramento, CA). The fourth input channel on the BIOPAC was used to capture a trigger
signal from the scanner given at the beginning of each brain volume acquisition. These
inputs were digitally sampled at 500 Hz and the resulting data was stored on an attached computer running BIOPAC Student Lab Pro software version 3.7.0 (BIOPAC Systems). The time scales for all four acquisition channels were synchronized, so the amplitude of each physiologic parameter relative to the time of each image acquisition could be precisely determined. Temporal filtering of the physiologic data was performed with AcqKnowledge version 3.5.7 (BIOPAC Systems). The RB and PPG data were both low-pass filtered using a digital infinite impulse response filter with a cutoff of 2 Hz to remove high frequency signal fluctuations caused by interference from the rapid switching of the gradient magnets. The filtered physiologic waveforms from all scans were visually examined for errors and any that showed periods lacking data were excluded from further analysis.

The three physiologic waveforms were processed with custom code implemented in MATLAB (The Math Works, Natick, MA) that is included in Appendix C. The acquired capnograph was time-shifted by 8.2 s to account for the constant time delay for the expired air to traverse the sampling tubing and reach the gas monitor. The peak value at the end of each expiration, which is defined as the ETCO₂ value, was determined using a 2 s window. In this way, one ETCO₂ value per breath was extracted from the expired CO₂ waveform. The resulting ETCO₂ timecourse was parsed for incomplete breaths in which the peak value did not reflect a full expiration and these values were replaced with the average value of the previous and subsequent ETCO₂ value. These ETCO₂ values with known timing relative to each TR acquisition window were interpolated to the beginning of each TR interval, giving one value per image volume.
For each breath in the respiratory timecourse, the RVT value was calculated, as previously described (Birn et al., 2008). The peak and trough of the RB timecourse for each breath was determined, along with the peak to peak respiratory period. These values were independently interpolated to the beginning of each TR interval. The RVT was calculated for each TR as the difference in respiration amplitude (peak minus trough) divided by the peak to peak respiratory period. Thus, \( RVT = \frac{(R_{\text{peak}} - R_{\text{trough}})}{TPP} \), as shown in Fig. 3.1.

For the breathing modulation experiment, the values of ETCO₂ and RVT during each experimental condition were compared to the other conditions to assess whether changes in paced breathing were reflected in significant ETCO₂ and RVT differences between conditions. A linear mixed effects model was used for comparisons, which accounts for intrasubject temporal dependence. The Holm-Bonferroni method to correct for multiple comparisons was used to keep the total family-wise error rate at \( \alpha = 0.05 \).

The RB and PPG timecourses were processed to format them for input to a slice-specific version of the RETROICOR physiologic noise correction algorithm (Glover et al., 2000), modified to account for the 500Hz sampling rate and the interleaved slice acquisition order. The portions of the physiologic timecourses that corresponded to the image acquisition window were determined from the scanner trigger signals and only these data were processed for RETROICOR correction. All peaks in the PPG data were found using a 0.5 s window and the peak location replaced with a flag value of –1000. The RB timecourse values were rescaled to unsigned integers between 0 and 32,000.

Before further processing, image data were preprocessed offline using FSL (Smith et al., 2004) version 4.1.1. This included brain extraction (Smith, 2002), spatial
smoothing using a Gaussian kernel of full-width at half-maximum (FWHM) of 7 mm, highpass temporal filtering with a cutoff period of 60 s, and motion correction using linear registration (Jenkinson et al., 2002). Motion of more than half the voxel dimension (> 1.875 mm) was a criterion used to exclude a dataset from further analysis. Slice-timing correction and pre-whitening were not used in the data analysis.

To determine the optimal response function for ETCO₂-induced MR signal changes, the interpolated ETCO₂ timecourse was convolved with a number of impulse response functions in which the five parameters shown in Fig. 3.2 were systematically varied. The different response function shapes were generated in MATLAB using the fmridesign() function from the FMRIstat analysis package (Worsley et al., 2002). This convolved ETCO₂ timecourse was then linearly regressed against each brain voxel timeseries and the F-statistic, coefficient of multiple determination (R², indicating goodness of model fit), and significance level (p) were determined and saved in 3-D maps for each subject. The algorithms for the ETCO₂ regression analysis are shown in Appendix D. Those voxels with p < 0.05 were considered to have MR signal timecourses significantly correlated to the regressor and results from these voxels are included in the summary of a particular regression analysis. The average ETCO₂ response function was optimized iteratively by modifying the response function parameters until a maximum was found in the mean F-statistic and R² value averaged across each subject’s brain and then across subjects.

A further analysis of the robustness of this response function was performed by time-shifting the ETCO₂ values over a range of −4 to 16 s in 0.5 s increments prior to interpolation and convolution. This range was the maximum possible for all subjects,
given the duration of physiologic data recorded prior to and after image acquisition, accounting for the expired CO₂ sampling delay. This latency analysis allowed examination of the heterogeneity across brain regions of the delay between ETCO₂ changes and MR signal fluctuations. For each subject, a 3-D map of the best-fit delay time for each voxel was created based on the maximum F-statistic across all delay times representing the strongest correlation.

For comparison, the RVT values were processed similarly to the ETCO₂ values. The respiratory response function (RRF), which is optimized for relating changes in RVT to MR signal changes (Birn et al., 2008) was plotted and the peak timings, amplitudes, and widths were determined graphically. The RRF was implemented in MATLAB using the `fmridesign()` function using the parameters (corresponding to the notation in Fig. 3.2) [3.07, 4.19, 15.44, 17.42, 1.115]. This optimized response function was convolved with the interpolated RVT timecourse and the resulting convolved timecourse was regressed against the MR data timecourse in each voxel separately and in the same fashion as described above for ETCO₂. Given the duration of RB data recorded prior to and after functional image acquisition, the range of –10 to 10 s (0.5 s increments) was used for the RVT latency analysis.

The ETCO₂ and RVT timecourses convolved with their optimal average response functions were used as model inputs to FEAT version 5.98 (part of FSL 4.1.1). Time-series statistical analysis was carried out using FILM (Woolrich et al., 2001). No further convolution was performed and no additional model terms were included in the analysis for the breathing modulation experiment. Pain data analysis also included a temporal model of the block-design pain stimulus timing, along with its first derivative, to account
for possible imperfections in stimulus delivery onset times. Derivative terms were not necessary for the ETCO₂ or RVT regressors. Individual subject images were registered to the MNI standard space brain (Jenkinson et al., 2002). Group average maps were created with a fixed effects model using FLAME (Beckmann et al., 2003; Woolrich et al., 2004b). Group maps were thresholded using clusters determined by $Z > 3.0$ and a cluster significance threshold of $p < 0.05$, corrected for multiple comparisons.

The FSL analysis was repeated with flexible response functions created using the FMRIB Linear Optimal Basis Set (FLOBS) utility (Woolrich et al., 2004a). In this analysis, a set of three basis functions was created, separately for ETCO₂ and RVT, based on the shapes of the previously determined optimal response functions, but allowing a ±2 s range for all timing parameters. In effect, this allows a different shape response function to be applied to each voxel. Resulting group maps were determined using the same methods as described above.

3.3 Results

In the breathing modulation experiment, initial analysis of the data from subject #3 showed motion of 2.5 mm, which is greater than half of the voxel dimension, and was thus excluded from further analysis. The remaining eight subjects showed motion of 1.5 mm or less, and consisted of three males with mean age 29.3 ± 10.2 (standard deviation) and age range 23 to 53 years. All subjects’ respiratory patterns changed in response to the experimental cues, resulting in well-defined respiratory and ETCO₂ changes. The RB and ETCO₂ plots for the entire experiment for one subject are shown in Fig. 3.3.
Averaging across subjects, changes in both ETCO$_2$ and RVT occurred between the different conditions of the breathing modulation experiment, as shown in Fig 3.4. The two timecourses were inversely correlated to one another ($r = -0.61$). Compared to the baseline levels during the initial free breathing period, a 35% ETCO$_2$ decrease was seen in the Rapid & Deep condition. The ETCO$_2$ levels during the Rapid1, Deep1, and Rapid & Deep conditions were significantly lower ($p < 0.05$) than those in the preceding condition. Also, the ETCO$_2$ levels during each breathing condition following the Rapid & Deep condition were significantly lower than in the first occurrence of the corresponding condition. The RVT timecourse also showed significant changes between different paced breathing tasks. A 105% increase in RVT was seen between the Free1 and Rapid & Deep conditions. In parallel to the identical breathing patterns cues in repeated conditions, the RVT timecourse showed no significant differences ($p > 0.05$) between the first and second occurrences of the Free, Normal, Rapid, Deep, and Rapid & Deep conditions. Looking at consecutive conditions, the RVT significantly differed between the Normal1 and Rapid1 conditions and between the Deep1 and Rapid & Deep conditions.

Some representative results from the iterative optimization process are listed in Table 3.2. The mean $R^2$ value was used primarily and the mean F-statistic was used secondarily as the metrics to determine the best model fit. The analysis began with two hemodynamic response functions (Cohen, 1997; Glover, 1999) and the respiratory response function (Birn et al., 2008) as possible starting points. It was initially found that the double gamma function (Glover, 1999) provided the best fit, so the parameters were individually modified in the direction of increasing the mean $R^2$ and mean F-statistic. The
optimal ETCO$_2$ response function parameters, shown highlighted gray in Table 3.2, were found to be [12, 7, 26, 9, 0.7], using the notation described in Fig. 3.2. These parameters give a transfer function with the shape plotted in Fig. 3.5. The analyses following the highlighted row verify that incremental increases or decreases in any of the response function parameters result in a sub-optimal fit, indicated by the smaller F-statistic and R$^2$ values. The individual subject values for the optimal parameters are shown in Table 3.3.

The latency analysis, which varied the delay between the ETCO$_2$ and FMRI timecourses, showed different results for each subject. Several slices of the spatial maps of delay time at which strongest correlation occurred are shown for each subject in Fig. 3.6. The mean calculated across each subject’s brain of these best fit delay times, as well as the corresponding F-statistic and R$^2$, are listed in Table 3.4. A histogram showing the all-subject average number of voxels with best-fit ETCO$_2$ regression occurring at each delay value is included as Fig. 3.7. The histogram bins match the increments described in the methods, –4 to 16 s in 0.5 s increments.

The individual subject summary values from regression of the RVT timecourse convolved with the RRF against the acquired breathing modulation MR data are listed in Table 3.5. Comparing to the ETCO$_2$ results in Table 3.3, the RVT regressors were, on average, less strongly correlated to the FMRI data than the ETCO$_2$ regressors when comparing the number of voxels significantly correlated (6084 vs. 13417), the mean F-statistic (7.36 vs. 11.52), or mean R$^2$ (0.0337 vs. 0.0509). The results of the latency analysis for RVT are listed in Table 3.6 and a similar case can be made for weaker correlation of RVT compared to ETCO$_2$ (compare to Table 3.4). The average delay value of the best model fit varied widely across subjects for RVT, as it did for ETCO$_2$. The
spatial maps of delay time at which strongest correlation occurred are shown for each subject in Fig. 3.8. A histogram showing the all-subject average number of voxels with best-fit RVT regression occurring at each delay value is included as Fig. 3.9. The histogram bins match the increments in the algorithm described in the methods.

The four panels of Fig. 3.10 show the group average FSL maps for the breathing modulation experiment, overlaid on the MNI standard brain. Highlighted voxels are correlated to either the ETCO₂ or RVT timecourse convolved with their respective optimized response functions both without and with flexibility across voxels (using the FLOBS utility). The ETCO₂ model with a fixed response function for all voxels, shown in panel A, was more strongly (max Z = 11.8) and diffusely (212,351 voxels) correlated to the FMRI data than the equivalent RVT model in panel C (max Z = 7.43, with 40,089 significant voxels). Allowing a flexible response function with the FLOBS utility for ETCO₂ (panel B) decreased the statistical score by 17.8% (max Z = 9.7), while increasing the number of significant voxels 5.7% (225,095 correlated). The RVT map with FLOBS (panel D) had a 5.5% decrease in Z-score (max Z = 7.02) but the extent of activation increased by 261.0% (144,733 significant voxels).

In the pain experiment, both scans from one subject and one scan from two of the subjects showed motion of ≥ 2 mm. Two different subjects had failures of some aspect of the physiologic data recording for both scans that went undetected during data acquisition. The remaining ten complete FMRI and physiologic datasets were used for subsequent analysis. The six subjects from which this usable data was obtained consisted of four males with average age 31.8 ± 11.3 (standard deviation) and age range 23 to 53 years. Changes in ETCO₂ and RVT throughout the pain experiment are shown in Fig.
3.11. In contrast to the previous results shown in Appendix A, no significant changes in ETCO₂ or RVT were demonstrated in the data from this pain experiment.

The four panels of Fig. 3.12 show the group average FSL maps for the pain data, overlaid on the MNI standard brain. Highlighted voxels are correlated to either the ETCO₂ or RVT timecourse convolved with their respective optimized response function both without and with flexibility across voxels (using the FLOBS utility). The ETCO₂ model with a fixed response function for all voxels, shown in panel A, was less strongly (max \( Z = 7.22 \)) and less diffusely (23,153 voxels) correlated to the FMRI data than the equivalent RVT model in panel C (max \( Z = 9.91 \), with 97,644 significant voxels). Allowing a flexible response function with the FLOBS utility for ETCO₂ (panel B) decreased the statistical score by 24.38% (max \( Z = 5.46 \)), and decreased the number of significant voxels 49.6% (11,659 correlated). The RVT map with FLOBS (panel D) had a 6.0% decrease in Z-score (max \( Z = 9.32 \)) and an 11.5% decrease in the extent of activation by (86375 significant voxels).

3.4 Discussion

ETCO₂ is highly correlated to arterial CO₂ but likely underestimates it at rest (Robbins et al., 1990; Barton and Wang, 1994). Since the arterial CO₂ concentration actually drives blood vessel diameter and thus CBF, a misestimation could confound our ability to detect correlation between ETCO₂ and FMRI data. However, it has been shown during hypocapnia that the ETCO₂ value does not underestimate arterial CO₂ (Barton and Wang, 1994). In the context of the breathing modulation experiment, this means that the change in arterial CO₂ level may have been even more pronounced than the measured
change in ETCO₂ but this change is not likely to have been underestimated. Furthermore, CBF (estimated by MCA blood flow velocity) is correlated to changes in ETCO₂ throughout the range of 20-50 mmHg (Ide et al., 2003), which includes (with wide margins) the values observed in both datasets in this study. Thus, the ETCO₂ data collected in these experiments is expected to be a reliable estimate of arterial CO₂.

Adaptation in the CBF response to prolonged hypocapnia was another possible confound to correlating ETCO₂ (and arterial CO₂) changes to BOLD signal changes. Such an adaptive response would occur if a slow change in vascular reactivity to CO₂ occurred during each constant breathing condition. This change could potentially cause non-linear CBF increases independent of the constant measured ETCO₂ level. However, this physiologic adaptation has a time constant of approximately 7 min during a constant level of hypocapnia (Poulin et al., 1998) and is thus not likely to have affected the breathing modulation experiment.

The end-tidal oxygen concentration was not recorded in this study, but is expected to increase slightly with hyperventilation. High levels of hyperoxia are associated with increased BOLD signal, likely due to a change in magnetic susceptibility resulting from an increase in dissolved molecular oxygen in blood (Kennan et al., 1997). Breathing 100% oxygen is associated with global (Rostrup et al., 1995) and local (Bulte et al., 2007) CBF increases. However, moderate levels of hyperoxia may not have detectable effects on either BOLD or flow-weighted images (Rostrup et al., 1995). The BOLD response to changes in end-tidal oxygen has recently been found to be 0.004 %/mmHg, which is 60 times smaller than the BOLD reactivity to ETCO₂ of 0.283 %/mmHg (Prisman et al., 2008). The authors concluded that accounting for end-tidal oxygen
changes in BOLD imaging is important only when ETCO₂ changes are small (Prisman et al., 2008). This data suggests that the small BOLD signal change from the mild hyperoxia induced by hyperventilation would be overshadowed by the large changes induced by the significant hypocapnia.

As an integral part of this study, a reasonable average linear transfer function between induced ETCO₂ variations and BOLD signal changes was determined. The assumption of linearity is commonly applied to more complex biologic events that can be approximated as linear systems under a certain range of conditions. One example is in FMRI, where linear systems analysis is a cornerstone in the analysis process (Boynton et al., 1996; Cohen, 1997). In determining task activation, the paradigm is convolved with a hemodynamic response function resulting in a regressor representing task timing and amplitude filtered by the resulting BOLD response. The inclusion of more detailed, non-linear physiologic models (Buxton et al., 1998) do have an impact on the results, but activation is detected equally well using a linear model in most cases (Deneux and Faugeras, 2006). The assumption of linearity requires a BOLD signal change in response to a given task resulting in neural stimulation to remain at a constant level until the task is concluded. Similarly, the RRF assumes that a change in RVT to a new constant level will be reflected by proportional change in the BOLD signal (Birn et al., 2008). Since no additional non-linearities are expected in the BOLD response to ETCO₂ changes, this study modeled ETCO₂ changes as a linear system.

The iterative analysis of the ETCO₂ and FMRI data collected in the breathing modulation experiment yielded a biphasic impulse response function. The first peak of the ETCO₂ response function occurs at 12 s with FWHM = 7 s. The second peak with
opposite polarity occurs at 26 s, is smaller in amplitude (relative ratio of 0.7), and is slightly broader, with FWHM = 9s. This response function shape shows greater delay of onset and larger effect of the second peak than the hemodynamic response functions commonly used to model task activation (Cohen, 1997; Glover, 1999). This disparity suggests that the BOLD response from a change in ETCO₂ takes more time to manifest than the BOLD response to neuronal activity. As a result, ETCO₂ is not optimally modeled using the default hemodynamic response functions available in most FMRI analysis packages.

The longer delay time for the ETCO₂ response function may also explain the differences between some results in the literature. For example, a sporadic but significant relationship between basal ETCO₂ changes and BOLD FMRI data was found using a gamma-variate response function with a mean lag of 6 s and a width of 6.3 s implemented in FSL (Wise et al., 2004). These parameters were based on empiric measurements of the delay between ETCO₂ changes and MCA blood flow changes. The optimized delay times obtained for the ETCO₂ response function are more consist with later work by the same group (Wise et al., 2007) and another study (van der Zande et al., 2005) which reported average delay times between a CO₂ challenge and BOLD signal changes in the brain parenchyma of 12 and 15 s, respectively. With 12 s peak delay in the ETCO₂ model, the correlation with the FMRI data was greatly increased and covered most of the cerebral cortex (Wise et al., 2007). The group average map in Fig. 3.10 (A) demonstrates a similarly widespread pattern of strong correlation using the optimized ETCO₂ response function, which also has an initial peak delay of 12 s. Thus, the determined ETCO₂ response function yields results consistent with previous reports (van
der Zande et al., 2005; Wise et al., 2007) suggesting that BOLD signal changes are seen approximately 12 s after a perturbation in ETCO₂. These changes occur 6-8 s after the corresponding changes in MCA blood flow velocity changes (Panerai et al., 2000; Wise et al., 2004). This additional delay includes the blood transit time from the supplying arteries to the draining venules responsible for the majority of the BOLD signal.

The novel ETCO₂ response function has a shape quite distinct from the respiration response function (RRF) optimized to model RVT changes. In fact, it was clear early in the optimization process that convolving the ETCO₂ data with the RRF resulted in a sub-optimal fit to the MR data (Table 3.2). This difference may seem unexpected, since RVT and ETCO₂ are presumably modeling similar effects, namely breathing-related changes in arterial CO₂ leading to CBF changes. However, it is important to note that changes in RVT are inversely correlated to changes in ETCO₂, as increased minute volume reflected in an increased RVT results in decreased ETCO₂. Thus, compared to the RRF, the ETCO₂ response function would be expected to have a transfer function with opposite polarity of the major peak. It is the second (negative) portion of the RRF, with peak occurring at approximately 15.4 s that has the larger amplitude (1.12x first peak) and is broader (FWHM = 17.4 s), representing a greater impact on BOLD signal changes from RVT. This second portion of the RRF corresponds to the first (larger amplitude) portion of the ETCO₂ response function, with peak occurring at 12 s. Additional differences between the two response functions are in the timing and width of their lesser amplitude components. For an RVT increase, an early and short-lived BOLD signal increase is modeled by the minor RRF peak at 3.1 s with FWHM = 4.2 s. For an ETCO₂ increase, a late BOLD signal decrease (undershoot) is modeled by the lesser peak of the ETCO₂
response function at 26 s with FWHM = 9 s. The overall duration of effect for the RRF is greater than 50 s, whereas the ETCO₂ response function returns to baseline by 40 s. It is possible that the fit of the ETCO₂ response function would be further improved by including an early third component analogous to the RRF peak at 3.1 s. However, such optimization was beyond this scope of this initial report in which a reasonably optimized two-component ETCO₂ transfer function was determined and validated for two FMRI datasets.

The design of the breathing modulation experiment effectively uncouples respiration from its positive feedback control mechanism driven by arterial CO₂ levels. This is accomplished by experimentally pacing breathing in excess of the respiratory drive. The hypocapnia induced by the end of the RAPID&DEEP condition persists throughout the second half of the experiment, resulting in lower ETCO₂ values but similar RVT values when comparing the first to the second occurrence of the NORMAL, RAPID, and DEEP conditions (Fig. 3.4). This uncoupling creates a disparity between changes in the RVT and the arterial CO₂ level it is intended to normally model. This results in the greater correlation to the MR data of ETCO₂ compared to RVT, which is clearly illustrated in Fig. 3.10 by comparing panel A to panel C. The pain stimulation paradigm used in acquiring the pain FMRI dataset has previously been shown to cause hyperventilation and significant reductions in ETCO₂ over the course of four repeated stimulations, as demonstrated in Appendix A. Nonetheless, such significant changes did not prevent RVT from modelling a more diffuse area of low-frequency changes in the pain FMRI data than ETCO₂, as shown in Fig. 3.12. This demonstration of RVT correlations to task FMRI data is consistent with the improvement in language task
activation detection when RVT correction was applied after RETROICOR (Birn et al., 2006). Both results support the use of RVT correction for FMRI of routine cognitive tasks, even if some ventilation changes are expected, as in pain. However, in studies where changes in end-tidal or arterial CO₂ are expected to be uncoupled from respiration due to the functional task, a disease process, or a pharmacologic intervention, the RVT calculated from the respiration waveform may be inadequate to model BOLD signal changes and ETCO₂ correction should be employed.

Variability in the BOLD response to task stimulation has been demonstrated across subjects and, to a lesser extent, between different brain regions (Aguirre et al., 1998; Miezin et al., 2000; Handwerker et al., 2004; Liu et al., 2005; Thomason et al., 2005). Partial volume effects related to microvascular anatomy in each voxel likely contributes to differences in the shape (peak time and width) of the response (de Zwart et al., 2005). Some of the same mechanisms likely contribute to the range of latencies observed in the BOLD response to RVT changes (Birn et al., 2006; Birn et al., 2008). Regional heterogeneity in the latency of the BOLD response to hypocapnia due to hyperventilation (Posse et al., 1997) and hypercapnia induced by breath-holding (Kastrup et al., 1999; Chang et al., 2008) further suggest that there may be differences in vascular CO₂-reactivity in different parts of the brain. All of these mechanisms may contribute to the variation in optimum delay time across different voxels and between subjects seen in the ETCO₂ (Fig. 3.6) and RVT (Fig. 3.8) latency analysis maps. The distribution across subjects in the average number of voxels at each delay time are roughly centered at zero for both ETCO₂ (Fig. 3.7) and RVT (Fig. 3.8). However, inter-subject variability is evident when comparing the different mean delay times across subjects listed in Table 3.4
(ETCO₂) and Table 3.6 (RVT). These differences suggested that a single response function for all voxels in the images of all subjects may not optimally model the BOLD response to changes in either ETCO₂ or RVT.

The FLOBS utility, available in the recent releases of FSL, allows flexibility in the response function used in the analysis at each voxel (Woolrich et al., 2004a). This utility creates multiple response function possibilities based on specification of a range of values for the delay times and amplitude ratio in a five parameter model. The shape of the response function estimates are constrained to have two peaks of opposite polarity, similar to all the response function shapes previously described. Flexible respiration and ETCO₂ response functions were generated using all the onset and peak times previously determined, but including ± 2 s range for each. The FLOBS algorithm created basis functions which were then used to independently model the ETCO₂ and RVT responses for every voxel in each subject’s image data. Because of the variability detected in the latency analysis both between and within subjects, it was anticipated that the FLOBS analysis would result in greater correlation between the physiologic and MR data. Counter-intuitively, the basis set models resulted in decreased average Z-scores for both ETCO₂ and RVT applied to either FMRI dataset using FSL. One possible explanation is a statistical penalty for the reduced degrees of freedom in applying three model functions per voxel, rather than only one. The effect of response function variability on the spatial extent of activation differed between the two FMRI datasets. For the breathing modulation dataset (Fig. 3.10), the FLOBS analysis caused a relative increase in significant voxels for both ETCO₂ (5.7%) and RVT (261.0%). For the pain dataset (Fig. 3.12), decreases of 49.6% (ETCO₂) and 11.5% (RVT) were seen in the number of
significant voxels when using FLOBS. These mixed results suggest that the average response functions are adequate models and that further work is needed to determine the benefit of including flexibility in the response function model across voxels and across subjects.

3.5 Conclusions

In this study, an optimized transfer function for ETCO₂ correction in BOLD FMRI is determined. The impact of implementing this correction was illustrated by applying it to two datasets with different tasks. It was shown that ETCO₂ fluctuations were more correlated to the image data acquired during paced hyperventilation than during repeated periods of painful electric nerve stimulation. Furthermore, using optimized response functions for both, ETCO₂ was more diffusely and strongly correlated to the breathing modulation data than the RVT. This indicates that ETCO₂ monitoring and correction may be necessary in FMRI when the breathing pattern is uncoupled from arterial CO₂ levels.
### 3.6 Tables and Figures

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Table 3.1. Description of conditions in breathing modulation experiment.
### Table 3.2. Results of iterative ETCO₂ response function regression in MATLAB. See Fig. 3.2 for a depiction of the response function parameters. The calculated regression statistics were calculated across each subject’s brain, then averaged across subjects. The mean count is the average number of voxels significantly correlated to the convolved ETCO₂ regressor.

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<th>IRF (Cohen 1997)</th>
<th>HRF (Glover 1999)</th>
<th>RRF (Birn 2008)</th>
<th>Modified HRF - 6s</th>
<th>Modified HRF - 9s</th>
<th>Modified HRF - 14s</th>
<th>Modified HRF - 13s</th>
<th>Modified HRF - 12s</th>
<th>Modified HRF - 11s</th>
<th>Modified HRF - 13s</th>
<th>Modified HRF - 12s</th>
<th>Modified HRF - 12s</th>
<th>Modified HRF - 12s</th>
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Table 3.3. Individual subject whole-brain average results for optimal CO₂ response function convolved with the ETCO₂ timecourse and regressed against the breathing modulation data. Signif. = statistically significant (p < 0.05), F-stat = F-statistic, Max = maximum.

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Table 3.4. Individual subject whole brain average results from regression analysis using multiple latencies between the ETCO₂ timecourse (convolved with the ETCO₂ response function) and MR data. F-stat = F-statistic, Max = maximum.

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</tr>
<tr>
<td>9</td>
<td>2114</td>
<td>19.54</td>
<td>5.99</td>
<td>0.0859</td>
<td>0.0279</td>
</tr>
<tr>
<td>Average</td>
<td>6084</td>
<td>36.67</td>
<td>7.36</td>
<td>0.1436</td>
<td>0.0337</td>
</tr>
</tbody>
</table>

Table 3.5. Individual subject whole-brain average results for the RRF convolved with the RVT timecourse and regressed against the breathing modulation data. Signif. = statistically significant ($p < 0.05$), F-stat = F-statistic, Max = maximum.

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Mean Delay</th>
<th>Max F-stat</th>
<th>Mean F-stat</th>
<th>Max $R^2$</th>
<th>Mean $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.35</td>
<td>50.42</td>
<td>8.83</td>
<td>0.1951</td>
<td>0.0403</td>
</tr>
<tr>
<td>2</td>
<td>-3.76</td>
<td>38.97</td>
<td>7.33</td>
<td>0.1578</td>
<td>0.0337</td>
</tr>
<tr>
<td>4</td>
<td>0.32</td>
<td>105.34</td>
<td>12.47</td>
<td>0.3362</td>
<td>0.0549</td>
</tr>
<tr>
<td>5</td>
<td>0.23</td>
<td>17.40</td>
<td>5.93</td>
<td>0.0772</td>
<td>0.0276</td>
</tr>
<tr>
<td>6</td>
<td>-0.49</td>
<td>22.09</td>
<td>5.76</td>
<td>0.0960</td>
<td>0.0269</td>
</tr>
<tr>
<td>7</td>
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<td>34.93</td>
<td>7.56</td>
<td>0.1438</td>
<td>0.0348</td>
</tr>
<tr>
<td>8</td>
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<td>7.88</td>
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<td>0.0362</td>
</tr>
<tr>
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<td>0.0295</td>
</tr>
<tr>
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<td>-2.30</td>
<td>41.91</td>
<td>7.76</td>
<td>0.1597</td>
<td>0.0355</td>
</tr>
</tbody>
</table>

Table 3.6. Individual subject whole brain average results from regression analysis using multiple latencies between the RVT timecourse (convolved with the RRF) and MR data. F-stat = F-statistic, Max = maximum.
Figure 3.1. Graphical depiction of variables used in RVT calculation. $R_p$ = respiratory peak amplitude, $R_T$ = respiratory trough amplitude, $T_{pp}$ = peak to peak respiratory period.

Figure 3.2. Diagram of generic double-gamma function used to determine the optimal ETCO$_2$ response function. RF = response function, FWHM = full width at half maximum.
Figure 3.3. Plot of respiratory belt (RB, shown in red) and expired CO\textsubscript{2} (CO\textsubscript{2}, shown in green) amplitude for an exemplary subject throughout the breathing modulation experiment.

Figure 3.4. Plot of average ETCO\textsubscript{2} (red) and RVT (blue) timecourses for all subjects throughout the breathing modulation experiment. Error bars represent standard error of the mean. The labels immediately above the x-axis refer to the different breathing conditions described in Table 3.1.
Figure 3.5. Plot of the determined optimal ETCO$_2$ impulse response function. The vertical axis is in arbitrary amplitude units.
Figure 3.6. Maps of delay time for best fit regression in latency analysis for ETCO₂. Selected slices from the individual subjects are arranged in rows.
Figure 3.7. Histogram showing all-subject average number of voxels with best-fit ETCO$_2$ regression occurring at each delay value (–4 to 16 s, in 0.5 s increments). Error bars show the standard error. The mean (standard error) value at –4 s delay was 2743 (819.5); the overall y-axis scale was adjusted to clearly display the values at all other delay times.
Figure 3.8. Maps of delay time for best fit regression in latency analysis for RVT. Selected slices from the individual subjects are arranged in rows.
Figure 3.9. Histogram showing all-subject average number of voxels with best-fit RVT regression occurring at each delay value (–10 to 10 s, in 0.5 s increments). Error bars show the standard error. The mean (standard error) value at –10 s delay was 1524 (342.2); the overall y-axis scale was adjusted to clearly display the values at all other delay times.
Figure 3.10. Group average FSL maps for the breathing modulation experiment overlaid on the MNI standard brain. Voxels highlighted are correlated to the ETCO₂ (A & B) and RVT (C & D) timecourse convolved with their respective optimized response functions both without (A & C) and with (B & D) flexibility across voxels (using the FLOBS utility). Colorbar range is Z = 3 to 10.
Figure 3.11. Plot of average ETCO2 (red) and RVT (blue) timecourses for all subjects throughout the pain experiment. Error bars represent the standard error.
Figure 3.12. Group average FSL maps for the pain experiment overlaid on the MNI standard brain. Voxels highlighted are correlated to the ETCO₂ (A & B) and RVT (C & D) timecourse convolved with their respective optimized response functions both without (A & C) and with (B & D) flexibility across voxels (using the FLOBS utility). Colorbar range is $Z = 3$ to 10.
CHAPTER 4

THE EFFECTS OF PHYSIOLOGIC NOISE CORRECTION IN PAIN FUNCTIONAL MRI ACROSS FIELD STRENGTH

4.1 Introduction

Since its inception over 15 years ago (Belliveau et al., 1991; Ogawa et al., 1992), functional magnetic resonance imaging (FMRI) has grown tremendously in both ubiquity of use and precision of results. However, there remain fundamental limitations due to hardware constraints, the inherent variability between subjects, and noise in the acquired data. This chapter focuses on reducing noise in blood oxygen-level dependent (BOLD) FMRI to improve the detection of brain activation in the acquired data. Much of the noise in FMRI data is from physiologic sources and the proportion of total signal noise due to physiologic fluctuations increases at 3.0 T compared to 1.5 T (Kruger and Glover, 2001). This suggests that some of the benefits of performing functional imaging at higher field strength may be tempered by increases in noise proportional to field strength (Kruger et al., 2001). While some physiologic noise results from microscopic fluctuations in brain metabolic activity that cannot be directly quantified (Kruger and Glover, 2001), this chapter focuses on the quantifiable physiologic variations (mostly of respiratory and cardiac origin) that can be eliminated from the image data prior to analysis. Detecting physiologic changes of interest, including neuronal activity (Heeger
and Ress, 2002) and vascular response (Kastrup et al., 2001), should be improved by reducing the physiologic noise in the FMRI data.

Initial works on physiologic noise correction employed band-reject filtering (Biswal et al., 1996) and correction that operated on the raw (k-space) data (Hu et al., 1995). These corrections, like many modern techniques use externally measured respiratory and cardiac monitoring data. Respiratory data is usually collected from the subject with a respiratory belt (RB) or bellows and cardiac data is often from a pulse plethysmograph (PPG) sensor placed on one of the subject’s fingers. A variety of techniques have been developed that extract physiologic information from the MR data (Le and Hu, 1996; Chuang and Chen, 2001; Beall and Lowe, 2007; Cheng and Li, 2008), but none of these have become routinely implemented in functional imaging studies.

The physiologic noise correction algorithm most commonly implemented for FMRI is RETROICOR (Glover et al., 2000). This technique generates Fourier series regressors based on the phase of the respiratory and cardiac cycle at each image acquisition using simultaneously acquired physiologic data from RB and PPG sensors. The regressors from the RETORICOR algorithm can be applied to the FMRI data during pre-processing (Glover et al., 2000) or included in the general linear model (GLM) framework that is used to detect effects of interest (usually activation) along with other noise regressors such as motion parameters (Lund et al., 2006). Additionally, low-frequency changes in the FMRI timecourse not explained by the cyclic RETROICOR regressors may be removed with additional processing of the respiratory (Birn et al., 2006) or cardiac (Shmueli et al., 2007) timeseries. Another source of physiologic noise results from the slow changes in cerebral blood flow (CBF) during scanning that are
correlated to changes in respiration. Correlation between end-tidal carbon dioxide (ETCO₂) fluctuations and BOLD signal changes illustrates this noise (Wise et al., 2004), which under some experimental conditions can be estimated from the RB waveform (Birn et al., 2008). The novel application of general signal processing techniques such as adaptive filtering (Deckers et al., 2006) or deconvolution (Chang et al., 2009) to FMRI analysis can perform as well as or better than RETROICOR at removing noise. Ultimately, more insight into the impact of noise correction techniques is needed to discover the optimal set of techniques for physiologic noise correction for a given FMRI experiment.

This study quantifies the effects of RETROICOR applied to data at different field strengths with an addition and a modification from its conventional implementation. The addition is that the expired end-tidal carbon dioxide (ETCO₂) concentration is used to explain low frequency respiration-induced cerebral blood flow changes that may further contaminate the MR signal. The modification is that a higher sampling rate for the cardiac and respiratory data is used and compared to the 40 Hz sampling for common native implementations of RETROICOR. This modified implementation also accounts for the interleaved slice acquisition order. In the context of these changes and the two field strengths being studied, the effects of physiologic noise correction are assessed for a pain task on temporal signal noise, model fit, and activation significance and extent. This work is novel in four ways: the quantification of physiologic noise correction across field strengths, the analysis of different input physiologic sampling rates and an interleaved slice order correction to RETROICOR, the inclusion of ETCO₂ correction in task FMRI,
and the quantification of physiologic noise correction in FMRI of pain, which has possible task-correlated changes in physiologic response.

4.2 Methods

Two pain FMRI datasets are analyzed in this study. The first is the dataset acquired at 1.5 T described in detail in Chapter 2. The work in this chapter involves a reanalysis of that image and physiologic data, for which acquisition parameters can be found in section 2.2. The second is the 3.0 T pain dataset described in Chapter 3. Overall, seven datasets acquired at 1.5 T and ten datasets acquired at 3.0 T are included in this comparative analysis. Different subjects participated in each experiment, but an identical 4.5 min stimulation paradigm was used while 90 volumes of FMRI data were acquired. Initial physiologic data processing, including temporal filtering, was performed as described in Chapter 3.

The physiologic waveforms collected during scanning were processed with custom code implemented in MATLAB (The Math Works, Natick, MA) as shown in Appendix C and described in the methods section of Chapter 3. However, some differences in processing were necessary with the physiologic data acquired in the 1.5 T experiment. First, the 1.5 T scanner trigger signal was given at the beginning of each slice acquisition, rather than once per volume. A simple programming loop reducing the trigger frequency to once per volume was sufficient to format the trigger data to match that acquired on the 3.0 T scanner so the same processing code could be used. Due to a longer length of tubing, the expired CO₂ sampling delay was 17 s in the 1.5 T setup,
which was accounted for in all ETCO₂ calculations. Finally, the physiologic data was sampled at 200 Hz during the acquisition of the 1.5 T dataset and 500 Hz at 3.0 T.

The acquired capnographs were time-shifted by the measured time delay for the expired air to traverse the sampling tubing and reach the gas monitor. The peak value at the end of each expiration, which is equal to the ETCO₂ value, was determined using a ±1 s window. The resulting ETCO₂ timecourse was parsed for incomplete breaths in which the peak value did not reflect a full expiration and these values were replaced with the average value of the previous and subsequent ETCO₂ value. These ETCO₂ values were interpolated to the beginning of each TR interval, giving one value per image volume with fixed timing relative to all slice acquisitions.

The RB and PPG timecourses were processed to format them for input to a slice-specific version of the RETROICOR physiologic noise correction algorithm (provided by Jacco A. de Zwart of the National Institutes of Health, with permission from Gary H. Glover of Stanford University). The portions of the physiologic timecourses that corresponded to the image acquisition window were determined from the scanner trigger signals and only these data were processed for RETROICOR correction. In implementing the RETROICOR script as received, the physiologic data was downsampled to 40 Hz before further processing. This native implementation should reflect the manner in which RETROICOR is commonly applied by many FMRI researchers. All peaks in the PPG data were found using a 0.5 s window and the peak location replaced with a flag value of –1000. The RB timecourse values were rescaled to unsigned integers between 0 and 32,000. A modified implementation of RETROICOR was also created to assess the impact of physiologic data sampling rate and interleaved
slice acquisition order on noise correction. This second implementation accounted for the higher physiologic data sampling rate (200 Hz at 1.5 T and 500 Hz at 3.0 T) and the interleaved slice acquisition order in both acquired datasets. Since RETROICOR was expected to perform as well or better with these modifications, data from this modified implementation was used for all comparisons (unless otherwise specified).

Before further processing, image data were preprocessed offline with FSL (Smith et al., 2004) version 4.1.1. This included brain extraction (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width at half-maximum of 7 mm, highpass temporal filtering with a period cutoff of 60 s, and motion correction using linear registration (Jenkinson et al., 2002). Motion of more than half the voxel dimension (>1.875 mm) was the criterion used to exclude a dataset from further analysis. Slice-timing correction and pre-whitening were not used as part of the data analysis pipeline.

FMRI data was analyzed for pain activation with different combinations of physiologic noise correction applied after pre-processing: RB correction, PPG correction, RB + PPG correction, and RB + PPG + ETCO₂ correction. RB and PPG corrections were performed using the two versions of RETROICOR described above. ETCO₂ correction was performed by convolving the interpolated ETCO₂ timecourse with the optimal response function determined in chapter 3, regressing the result against each voxel timeseries and subtracting the significantly correlated (p < 0.05) portion from the data.

Functional analysis was performed on each voxel timeseries with FEAT version 5.98 (part of FSL 4.1.1) using FILM (Woolrich et al., 2001). The timing of the block-design pain stimulation paradigm was the primary model input, convolved with the
default hemodynamic response function. The first derivative of the pain stimulation paradigm was also included as an effect of no interest, to account for variability in the shape of the hemodynamic response function or imperfections in stimulus delivery timing (Handwerker et al., 2004). Individual subject images were registered to the MNI standard space brain (Jenkinson et al., 2002). Group average maps were created with a fixed effects model using FLAME (Beckmann et al., 2003; Woolrich et al., 2004b). Group maps were thresholded using clusters determined by \( Z > 2.0 \) and a cluster significance threshold of \( p < 0.05 \), corrected for multiple comparisons.

Summary statistics were calculated at each voxel in the individual subject functional-space brain-extracted images before and after each correction or combination of corrections was applied. These were then averaged across each subject’s brain and then averaged across subjects. The timecourse noise, indicated by \( \sigma \), was calculated as the standard deviation of the FMRI data in each voxel in the time dimension. Using the residuals from model fitting, the adjusted coefficient of multiple determination \( (R^2_a) \) was calculated for each voxel. The \( R^2_a \) value indicates goodness of model fit (Razavi et al., 2003) and is adjusted for the number of regressors used in the GLM, such that the term will decrease with the addition of an explanatory variable that does not explain its share of the variance in the data being modeled. To summarize the differences between models, the maximum and mean \( R^2_a \) values were determined for all subjects then averaged across subjects. Finally, the statistically thresholded individual subject activation maps were processed to determine the number of activated voxels and maximum Z-score for each combination of noise correction. The average values across subjects are listed for these metrics as well. A sample of the MATLAB code used to
calculate these summary statistics is provided in Appendix E. For statistical comparisons, a two-sample t-test (assuming unequal variance) was used, unless otherwise noted.

4.3 Results

Table 4.1 shows the summary statistics for the different combinations of noise correction applied at both field strengths. Comparing the average results across field strengths shows that temporal signal noise, model fit, statistical score, and percent brain activation were all greater at 3.0 T than at 1.5 T. It should also be noted that the variability between subjects, as indicated by the across-subject standard deviation, was generally, although not always, greater at 3.0 T. Differences between each noise correction combination are listed in Table 4.2 as magnitude and percent change. In both tables, the modified implementation of RETROICOR was used with 200Hz physiologic sampling in the 1.5 T dataset and 500 Hz sampling in the 3.0 T dataset and both accounted for the interleaved slice acquisition order.

The application of each noise correction or combination thereof reduced the temporal signal noise, $\sigma$. The greatest reduction in $\sigma$ was seen with all corrections applied ("Full correction vs. none” in Table 4.2) at both 1.5 T (–9.86%) and 3.0 T (–12.54%). At both field strengths, RETROICOR including both RB and PPG regressors caused a greater reduction in $\sigma$ than either the RB or PPG component applied individually, indicating a synergistic effect of both corrections applied together. The further reduction in $\sigma$ with the application of ETCO2 correction ("Full correction vs. [RB + PPG]” in Table 4.2) showed a greater reduction in $\sigma$ than either RB or PPG component
of RETROICOR correction applied individually, but 5-fold less change compared to the combined RB+PPG RETROICOR algorithm, at both field strengths. To summarize the σ results from Table 4.1 and Table 4.2, temporal signal noise is significantly greater at higher field strength (p = 0.011), and there is a significantly greater reduction in this noise measure with physiologic noise correction applied to data acquired at higher field (p = 0.013).

Changes in model fit (R²ₐ) with noise correction were generally positive, indicating an improvement in the ability to detect activation due to the pain stimulus. The maximum R²ₐ refers to the voxel in the brain with the best model fit, which is not necessarily the same voxel between model comparisons. The mean R²ₐ indicates the average model fit over the entire brain of each subject, including areas that are not strongly activated by the pain stimulus. The R²ₐ data parallels the changes in σ, as improvements due to the individual RB or PPG components of RETROICOR are overshadowed by larger increases with combined RB+PPG correction. The impact of ETCO₂ correction on model fit was markedly less than the other corrections at 3.0 T and it actually caused a decrease in both maximum and mean R²ₐ in the 1.5 T data. On average, RETROICOR improves model fit by 240% at 3.0 T, which is significantly (p < 0.0001) greater than the 227% improvement at 1.5 T.

The maximum Z score in the activation maps were significantly higher in the 3.0 T dataset (p < 0.0001). This score decreased when implementing any physiologic noise correction, with the exception of the slight increase with RB correction at 3.0 T. The application of ETCO₂ correction to the 1.5 T dataset caused a 34.2% decrease in maximum Z score (“Full correction vs. [RB+PPG]” in Table 4.2). When applied to the
3.0 T dataset, the reduction due to ETCO₂ correction was < 1%. The effect of RETROICOR (combined RB + PPG) correction on maximum Z-score did not differ between the two field strengths (p = 0.49).

The differences in the percentage of brain activation for each noise correction combination studied is listed in the final column of Table 4.2. Each noise correction caused a decrease in activation and these reductions were greater with additional corrections. The activation extent was greater at 3.0 T (p < 0.001) and the change in activation with RETROICOR correction was not significantly different between field strengths (p = 0.42). A very similar synergy was seen with the other summary statistics, the decrease in the percent activation with combined RB+PPG RETROICOR correction was greater than with either component applied individually.

A comparison of the performance of the two implementations of the RETROICOR algorithm, which are described in the methods, is shown in Table 4.3. The ETCO₂ correction was independent of the RETROICOR script, and was not included in this comparative analysis. The column headings in the table indicate the sampling rate of the physiologic data used as input to the RETROICOR algorithm. However, as mentioned, the modified implementations with the higher sampling rate (200 Hz at 1.5 T and 500 Hz at 3.0 T) also included a correction for the interleaved slice acquisition order. Generally, the change in the summary statistics with correction was similar using either technique. Only the maximum Z-score decrease with correction at 1.5 T was significantly different between implementations, with a greater decrease seen with the native 40 Hz implementation (p = 0.015).
The final noise correction analysis to be made here is between RETROICOR and the respiratory and cardiac corrections used in the RetroSLICE algorithm described in chapter 2. The changes in maximum $R^2_a$ and percent brain activation were similar with the application of either noise correction routine. However, RETROICOR outperformed RetroSLICE in the other two measures listed in Table 4.4. Specifically, RETROICOR caused a 3.5 fold larger increase in mean $R^2_a$ than RetroSLICE, which was significantly greater ($p < 0.0001$). The 8.2% decrease in $\sigma$ with RETROICOR was also significantly greater ($p = 0.024$) than the 5.4% reduction with RetroSLICE.

Finally, Fig. 4.1 shows how the group average activation maps from the data collected at both field strengths are modulated by physiologic noise correction. The distribution of brain areas activated in response to the painful stimulus is generally consistent with previous reports (Peyron et al., 2000; Apkarian et al., 2005). In both datasets, bilateral activation was seen in the primary and secondary somatosensory cortices, insula, and prefrontal cortex. Additionally, the 1.5 T dataset showed activation in the left cerebellum, and bilateral thalamus. Each noise correction had some effect on the group activation maps. In the 1.5 T dataset, the predominant change was a decrease in activation caused by ETCO$_2$ correction (shown in yellow). This includes the removal of entire clusters of activation such as seen in the right prefrontal cortex and thalamus. The changes to the 3.0 T dataset were more subtle, with changes predominantly occurring on the periphery of activated clusters, and more commonly caused by combinations of corrections, such as RETROICOR with RB and PPG (pink) or all three corrections together (white).
4.4 Discussion

This is the first quantitative description of physiologic noise correction applied to a pain FMRI study and of physiologic noise correction applied at two field strengths. This study does not, however, include the systematic application and analysis of all possible noise correction approaches available. Rather, the commonly used noise correction algorithm, RETROICOR, is examined with modifications that were hypothesized to improve its performance: correction for the interleaved slice acquisition order and use of higher physiologic data sampling rate. In the publication initially describing RETROICOR (Glover et al., 2000), one slice of resting state FMRI data from 3 subjects was analyzed and a reduction was shown in the percent signal components in spectra typically associated with respiratory and cardiac frequencies. This reduction was shown to be greater than when applying a previously described technique, RETROKCOR (Hu et al., 1995). The temporal signal noise was also shown to decrease in some regions of the brain, but these changes were not statistically significant (Glover et al., 2000). Many of the subsequent quantitative analyses of the impact of RETROICOR have also been performed on resting-state FMRI data for functional connectivity analysis (Birn et al., 2006; Shmueli et al., 2007; Jones et al., 2008). In this study, RETROICOR is applied to pain task FMRI and several metrics are calculated: temporal signal noise, model fit, and strength and extent of activation. Each of these measures has been used previously in the literature to quantify the effects of physiologic noise correction and the average values of these summary statistics reported here provide a baseline to compare novel noise correction algorithms, other cognitive tasks, and higher field strength acquisitions.
A previous BOLD FMRI study showed an increase in physiologic noise at 3.0 T compared to 1.5 T that accompanies the gains in SNR and CNR that are also seen at higher field strength (Kruger et al., 2001). Despite this increase in noise, increases in activation extent accompanying the doubling of field strength were seen in the visual (44%) and motor (36%) cortices (Kruger et al., 2001). A similar study for a variety of other cognitive tasks showed increases in the extent of activation from 23 to 82% in different regions throughout the brain (Krasnow et al., 2003). The statistical significance of the detected activation also increases at higher field (Kruger et al., 2001). This is consistent with the results for no correction shown in Table 4.1. The significantly greater temporal signal noise at 3.0 T in this study is consistent with the idea that noise increases with increasing field strength. Despite this increased noise, the average uncorrected pain model fit (mean $R^2_a$) was 59% greater at 3.0 T compared to 1.5 T. The pain activation at 3.0 T covered 63% greater area and had a 24% larger Z-score than at 1.5 T. It is from these baseline values in the uncorrected analysis for each summary statistic at both field strengths that noise correction is explored.

Despite the important study of BOLD signal noise structure (Kruger and Glover, 2001) and several studies that examined FMRI results (Kruger et al., 2001; Krasnow et al., 2003; Tieleman et al., 2007; Meindl et al., 2008) at two field strengths, this is the first study comparing the impact of FMRI physiologic noise correction across two different field strengths. To summarize the results of Table 4.2 comparing field strengths, RETROICOR caused reductions in $\sigma$, increases in $R^2_a$, decreases in Z-score, and decreases in activation. In comparing respiratory and cardiac correction with RETROICOR across field strengths, the reductions in $\sigma$ and the increases in $R^2_a$ were
significantly greater at 3.0 T. This suggests that, in parallel with the increased physiologic noise and increased activation in uncorrected FMRI data acquired at higher field, physiologic noise correction has a greater effect on FMRI results at higher field.

To determine the individual impact of the RB and PPG components of RETROICOR, each was applied separately to the data. As shown in Table 4.2, the effects of RB and PPG correction on the summary statistics were generally similar in magnitude. The effect from the combined RETROICOR correction was always greater than either effect individually and usually greater than the sum of the individual effects. This indicates that both corrections performed together have a synergistic effect on the summary statistics examined here. An implication of this finding is that RETROICOR should be applied using both RB and PPG monitoring data in FMRI of pain.

The final noise correction listed in Table 4.1 and full correction comparisons listed in Table 4.2 include ETCO2 correction. Slow changes in breathing during FMRI scanning can cause BOLD signal fluctuations that are not cyclic, and thus not removed by RETROICOR correction (Birn et al., 2006). It is possible to correct for these changes using a measure of respiratory tidal volume changes (Birn et al., 2008). However, ETCO2 changes are a more direct representation of the arterial CO2 changes that drive the BOLD signal changes (Wise et al., 2004). This reasoning, coupled with the positive results from the ETCO2 correction employed in chapter 2, led to the inclusion of ETCO2 data as an additional noise regressor. However, in chapter 2 ETCO2 correction was applied in the general linear model, including convolution with the BOLD hemodynamic response function. The implementation described here used the optimal ETCO2 response function determined in chapter 3. Surprisingly, the application of ETCO2 correction in
this manner to the pain data in this study, with 2 exceptions (max $R^2_a$ and Max $Z$ at 1.5 T), had much less of an impact than RETROICOR. This small impact could have two possible explanations. Either the changes in ETCO$_2$ during the pain experiment were insignificant or the ETCO$_2$ response function, which was determined from a different dataset, did not generalize well to this pain FMRI data.

The original implementation of RETROICOR was written to accept as inputs 16-bit unsigned integer physiologic data sampled at 40 Hz (Glover et al., 2000). This is the native data format and sampling rate output by some scanner’s built-in physiologic monitoring hardware and has been used in recent implementations of RETROICOR (Birn et al., 2006; Deckers et al., 2006; Shmueli et al., 2007; Birn et al., 2008; Chang et al., 2009). However, the physiologic data in this study was collected with separate monitoring equipment and digitized at a much higher sampling rate (either 200 or 500 Hz). In order to use this data for RETROICOR correction, it was initially downsampled to 40 Hz for use in the native implementation. This was compared to a modified RETROICOR implementation, in which the code was edited to accept higher sampling rate inputs.

In data acquired at both field strengths, the MR image slices in each brain volume were collected in an interleaved fashion, a common practice in fast imaging sequences with no slice gap. As a result, the slices in anatomical order in each volume do not correspond to the consecutive physiologic samples taken during each volume acquisition. In the modified implementation of RETROICOR, the slices in the pre-processed FMRI data were systematically reordered to match the acquisition order before performing RETROICOR correction. After correction, the slices were replaced in their anatomic
order. This correction procedure aligns the image data with the corresponding physiologic data.

The modified RETROICOR implementation had two anticipated advantages that led to the formation of the hypothesis that it would outperform the native implementation. The first is that the peak times for the cardiac and respiratory cycles could be more precisely determined with increased sampling rate. This was anticipated to improve the accuracy of the phase calculations in the RETROICOR algorithm used to create the Fourier series applied to each voxel. The second is that the correction is applied to the slices based on physiologic data acquired at the same time. However, the comparison in Table 4.3 shows no significant differences between the two implementations for any of the summary statistics calculated, with one exception for the maximum Z-score at 1.5 T. This indicates that neither change in the modified algorithm caused a consistently significant improvement in the results. Assuming a maximum cardiac frequency of 2 Hz (120 beats/min) and a respiratory frequency of much less, sampling at 40 Hz is ten times the Nyquist rate for the physiologic data. As shown by the similar performance of both implementations, there appears to be no benefit to further sampling rate increases. In addition, accounting for the interleaved slice acquisition did not have a significant impact on the results. This is likely due to the nature of the voxel-wise Fourier series fitting in the RETROICOR algorithm. By assigning different weights to combinations of sinusoids that are 0, 90, or 180 degrees out of phase from one another, the algorithm allows a varying delay time between physiologic changes and MR signal changes. Thus, precisely aligning the image slices with the concomitantly acquired physiologic data did not greatly affect the results, presumably as the coefficients of the underlying Fourier series change.
to account for any timing differences. This also explains the robustness of RETROICOR to the inherent differences in timing between the pulse waveform in the finger and the heterogeneous delay times for BOLD signal changes throughout the brain.

A lack of robustness to varying delay times is the major limitation of the cardiac and respiratory corrections employed as part of the RetroSLICE algorithm described in chapter 2. RetroSLICE assumes an instantaneous noise contamination effect on the acquired MR data based on the physiologic data recorded at the same time. For the effects of respiratory-induced susceptibility changes in the brain (Raj et al., 2001), this is likely to hold true. However, changes in intrathoracic pressure throughout the respiratory cycle can also contribute a delayed effect on the BOLD signal through venous oxygenation oscillations (Windischberger et al., 2002). Blood transit time likely differs between the finger where the PPG is measured and the brain and almost certainly differs across the brain due to vascular anatomy. Cyclic pulsations in cerebrospinal fluid also reflect a delayed signal increase following cardiac systole (Dagli et al., 1999). These multiple effects of respiratory and cardiac noise at each voxel with different delay times across the brain are apparently better captured by the RETROICOR algorithm, which independently fits each voxel timeseries with a combination of sinusoids. This likely explains the better performance of RETROICOR over RetroSLICE for respiratory and cardiac correction in terms of temporal noise reduction and average model fit improvement (Table 4.4).

The generalizability of the results for physiologic noise correction in pain FMRI reported here to other functional tasks is unknown. However, unilateral pain stimulation causes activation of a distributed network of cortical and subcortical structures bilaterally.
(Coghill et al., 1999) that often overlaps with sensory and motor processing areas (Gelnar et al., 1999). The impact of physiologic noise correction shown here reflects the average over the entire brain including several clusters of activation. These activated areas are likely to vary in their physiologic noise contamination due to heterogeneity in vascular density, BOLD reactivity, and strength of neuronal response to stimulation. Nonetheless, since pain activation involves several areas, the average effects of noise correction in pain FMRI described here may be generalizable to other tasks activating similar brain regions. Additionally, the painful stimulus used in this study typically does not cause the robust BOLD response seen with visual and motor tasks (Kruger et al., 2001). Pain shares this lower BOLD contrast with many cognitive tasks of interest in basic and clinical research. As a result, the difficulty in detecting pain activation above the noise floor in the acquired signal may be similar to other tasks, as may be the impact of physiologic noise correction.

Recent FMRI studies of painful stimulation are numerous and include several different stimuli: cold or heat (Koyama et al., 2004; Kurata et al., 2005; Moulton et al., 2006; Bingel et al., 2007), laser stimulation (Bingel et al., 2004; Youell et al., 2004), and electric nerve stimulation (Alkire et al., 2004; Ibinson et al., 2004; Christmann et al., 2007). However, none of these pain studies employed a physiologic noise correction scheme, despite the appearance of several such techniques years earlier (Hu et al., 1995; Biswal et al., 1996; Glover et al., 2000). The importance of physiologic noise correction is expected to be accentuated with painful stimulation, which can cause changes in breathing rate and depth (Ibinson and Small, 2004), heart rate (Moltner et al., 1990), blood pressure (Schobel et al., 1996), CBF (Coghill et al., 1998; Ibinson, 2004) and
ETCO$_2$ (Ibinson and Small, 2004) that could be reflected by an increase in correctable physiologic noise. However, conflicting data has also recently arisen, showing no changes with pain stimulation in CBF (Owen et al., 2008). Similarly, as demonstrated in Fig. 3.11, there were no significant differences in the ETCO$_2$ levels between pain and rest periods and no first or second order trends in ETCO$_2$ throughout this 3T pain experiment when analyzed with a mixed effects linear model. Variability between subjects in their physiologic response to pain may explain some of these discrepancies. In any case, an analysis of the impact of physiologic noise reduction on a non-painful sensory task is beyond the scope of this study. However, such a comparison could be easily done in the future by calculating the same summary statistics reported in the tables in this chapter.

The pain activation maps from both field strengths (Fig. 4.1) demonstrate a bilateral network representing many brain structures known to be involved in pain processing. With careful examination, it is obvious that there are discordances between the activation maps from the two datasets, most notably in the cerebellum and thalamus. However, the differences in these maps are probably not a straightforward effect of acquisition magnetic field strength. Subtle differences in the activation maps for the same task performed at two different field strengths are common (Kruger et al., 2001; Krasnow et al., 2003; Tieleman et al., 2007; Meindl et al., 2008), but the explanation for these larger differences is most likely the inherent variability of pain FMRI results. A review (Apkarian et al., 2005) showed that of the pain FMRI studies in healthy adults found in the literature, only 38% showed thalamic activation and only 15% showed cerebellar activation, while a majority of studies showed activation in the primary and secondary somatosensory cortices and the insula. This is consistent with the maps shown
in Fig. 4.1 in that the areas consistently activated bilaterally in both maps (primary and secondary somatosensory cortices and the insula) are also activated in a majority of studies in the literature. On the other hand, the cerebellum and thalamus, which appear as activated in only the 1.5 T data are inconsistently reported as activated in the literature. This variability may be explained by differences in the inter-individual response to pain that manifest as average activation map discrepancies in different cohorts of subjects. Another explanation may be differences in noise in the data acquisitions.

Most of the group activation map changes seen when physiologic noise correction was applied involved slight changes to the periphery of activated clusters. Overall, the net change was a reduction activation, as indicated by the decreases in average percent activation (Table 4.2). However, local increases in both the significance and extent of activation can be seen with correction in Fig. 4.1. For examples, see the changes in the left secondary somatosensory cortex in the 1.5 T map (panel A, fifth slice from left, lower cluster on right side of image) and the right secondary somatosensory cortex in the 3.0 T map (panel B, fifth slice, lower cluster on left side of image).

The activation in the thalamus in the 1.5 T dataset is concerning for another reason: it is eliminated with ETCO₂ correction. The absence of thalamic activation is inconsistent with the known synapse of spinothalamic tract neurons in the ascending pain pathway and also with reports of thalamic activation in FMRI of pain (Peyron et al., 2000; Apkarian et al., 2005). However, it is important to correctly interpret FMRI activation maps; voxels showing activation have task-correlated signal changes that are significantly larger than the noise floor of the data, such that we can reliably conclude that activity is occurring in that location. The converse is not true; one cannot reliably
conclude that areas not included in an activation map lack significant activity (Buxton, 2002). The removal of thalamic activation by ETCO$_2$ correction, against the neuroanatomical expectation of pain-related activity there, simply indicates that the pain stimulation paradigm and ETCO$_2$ changes were correlated and subtracting the ETCO$_2$ changes from the data made the signal no longer significantly exceed the noise. The consistent temporal noise reductions ($\sigma$ decreases) and model fit improvements ($R^2_a$ increases) seen with noise correction applied indicate that, overall, more good than harm is being done.

4.5 Conclusions

This study demonstrated that RETROICOR reduces signal noise and improves model fit, but decreases the statistical significance and extent of brain activation when applied to a pain FMRI study. Theses results were unaffected by using physiologic data with a much higher sampling rate than 40 Hz and also by correcting for the interleaved slice acquisition order, which validates the use of RETROICOR in its original implementation. Signal noise was greater in data acquired at higher field strength, but physiologic noise reduction with RETROICOR correction was also greater at higher field. ETCO$_2$ correction using the optimized response function determined in chapter 3 was also explored for pain FMRI, but, surprisingly, found to be of secondary importance to RETROICOR correction.
### 4.6 Tables and Figures

<table>
<thead>
<tr>
<th>Correction Applied</th>
<th>σ (%)</th>
<th>Max $R_a^2$</th>
<th>Mean $R_a^2$</th>
<th>Max Z</th>
<th>Activation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.282 ± 0.055</td>
<td>0.4067 ± 0.0765</td>
<td>0.0360 ± 0.0047</td>
<td>5.37 ± 0.68</td>
<td>2.79 ± 1.60</td>
</tr>
<tr>
<td>RB</td>
<td>0.278 ± 0.055</td>
<td>0.4183 ± 0.0912</td>
<td>0.0564 ± 0.0040</td>
<td>5.26 ± 0.63</td>
<td>2.60 ± 1.55</td>
</tr>
<tr>
<td>1.5 T PPG</td>
<td>0.278 ± 0.055</td>
<td>0.4059 ± 0.0666</td>
<td>0.0568 ± 0.0048</td>
<td>5.22 ± 0.61</td>
<td>2.78 ± 1.76</td>
</tr>
<tr>
<td>RB + PPG</td>
<td>0.259 ± 0.054</td>
<td>0.5860 ± 0.2103</td>
<td>0.1177 ± 0.0289</td>
<td>5.21 ± 0.73</td>
<td>2.35 ± 1.40</td>
</tr>
<tr>
<td>RB + PPG + ETCO₂</td>
<td>0.254 ± 0.053</td>
<td>0.5706 ± 0.2244</td>
<td>0.1175 ± 0.0326</td>
<td>3.43 ± 2.40</td>
<td>2.14 ± 3.03</td>
</tr>
<tr>
<td>None</td>
<td>0.366 ± 0.114</td>
<td>0.4481 ± 0.0980</td>
<td>0.0572 ± 0.0246</td>
<td>6.67 ± 1.27</td>
<td>7.66 ± 5.71</td>
</tr>
<tr>
<td>RB</td>
<td>0.359 ± 0.113</td>
<td>0.4610 ± 0.0888</td>
<td>0.0783 ± 0.0247</td>
<td>6.67 ± 1.30</td>
<td>7.91 ± 5.72</td>
</tr>
<tr>
<td>3.0 T PPG</td>
<td>0.360 ± 0.113</td>
<td>0.4622 ± 0.0788</td>
<td>0.0765 ± 0.0255</td>
<td>6.64 ± 1.30</td>
<td>7.63 ± 5.71</td>
</tr>
<tr>
<td>RB + PPG</td>
<td>0.328 ± 0.104</td>
<td>0.7459 ± 0.0872</td>
<td>0.1946 ± 0.0531</td>
<td>6.31 ± 1.47</td>
<td>6.97 ± 4.88</td>
</tr>
<tr>
<td>RB + PPG + ETCO₂</td>
<td>0.320 ± 0.090</td>
<td>0.7522 ± 0.0718</td>
<td>0.2028 ± 0.0487</td>
<td>6.27 ± 1.56</td>
<td>6.82 ± 5.00</td>
</tr>
</tbody>
</table>

Table 4.1. Whole brain all subject averages ± across-subject standard deviation for measures of the impact of physiologic noise correction. $\sigma$ (%) = temporal standard deviation of the preprocessed FMRI data timecourse as a percentage of the total MR signal amplitude. Max and mean $R_a^2$ are the maximum and average adjusted coefficient of multiple determination found in the brain. Max Z = maximum Z-score from the thresholded activation map. Activation (%) is the number of activated voxels expressed as a percentage of the number of voxels in the brain.
Table 4.2. Comparisons between select correction combinations listed in Table 4.1. Values listed are difference (% change). Full correction refers to applying RB, PPG, and ETCO2 corrections.

<table>
<thead>
<tr>
<th>Correction Comparison</th>
<th>$\Delta\sigma$ (%)</th>
<th>$\Delta\text{Max}R^2_a$</th>
<th>$\Delta\text{Mean}R^2_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 T</td>
<td>3.0 T</td>
<td>1.5 T</td>
</tr>
<tr>
<td>RB vs. none</td>
<td>-0.0046 (-1.63)</td>
<td>-0.0071 (-1.93)</td>
<td>0.0117 (2.87)</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-0.0045 (-1.59)</td>
<td>-0.0058 (-1.59)</td>
<td>-0.0008 (-0.19)</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-0.0231 (-8.17)</td>
<td>-0.0379 (-10.35)</td>
<td>0.1793 (44.08)</td>
</tr>
<tr>
<td>Full correction vs. [RB + PPG]</td>
<td>-0.0048 (-1.84)</td>
<td>-0.0080 (-2.44)</td>
<td>-0.0153 (-2.62)</td>
</tr>
<tr>
<td>Full correction vs. none</td>
<td>-0.0279 (-9.86)</td>
<td>-0.0459 (-12.54)</td>
<td>0.1639 (40.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correction Comparison</th>
<th>$\Delta\text{Max}Z$</th>
<th>$\Delta\text{Activation}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 T</td>
<td>3.0 T</td>
</tr>
<tr>
<td>RB vs. none</td>
<td>-0.11 (-2.13)</td>
<td>0.01 (0.08)</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-0.16 (-2.93)</td>
<td>-0.02 (-0.38)</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-0.16 (-3.05)</td>
<td>-0.36 (-5.36)</td>
</tr>
<tr>
<td>Full correction vs. [RB + PPG]</td>
<td>-1.78 (-34.19)</td>
<td>-0.04 (-0.68)</td>
</tr>
<tr>
<td>Full correction vs. none</td>
<td>-1.94 (-36.20)</td>
<td>-0.40 (-6.01)</td>
</tr>
</tbody>
</table>
Table 4.3. Changes in summary statistics from physiologic noise correction using both implementations of RETROICOR, denoted by the sampling rate of input physiologic data. Values shown are % change for the correction comparison listed.

<table>
<thead>
<tr>
<th>Sampling Rate (Hz):</th>
<th>Δ σ (%)</th>
<th>Δ Max R^2_a</th>
<th>Δ Mean R^2_a</th>
<th>Δ MaxZ</th>
<th>Δ Activation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB vs. none</td>
<td>-1.60</td>
<td>-1.63</td>
<td>2.18</td>
<td>57.97</td>
<td>-0.41</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-1.68</td>
<td>-1.59</td>
<td>-0.48</td>
<td>56.39</td>
<td>-1.52</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-8.00</td>
<td>-8.17</td>
<td>41.28</td>
<td>224.72</td>
<td>-8.23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Rate (Hz):</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB vs. none</td>
<td>-1.97</td>
<td>-1.93</td>
<td>3.66</td>
<td>37.61</td>
<td>0.62</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-1.68</td>
<td>-1.59</td>
<td>1.95</td>
<td>33.73</td>
<td>-1.10</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-9.62</td>
<td>-10.35</td>
<td>64.90</td>
<td>230.63</td>
<td>-3.15</td>
</tr>
</tbody>
</table>
Table 4.4. Comparison of average results for RB and PPG corrections, applied to the same 1.5 T dataset, using RETROICOR and RetroSLICE. Values are listed as % change.

<table>
<thead>
<tr>
<th>Correction Comparison</th>
<th>% Δ σ RETROICOR</th>
<th>% Δ σ RetroSLICE</th>
<th>%Δ Max $R^2_+\alpha$ RETROICOR</th>
<th>%Δ Max $R^2_+\alpha$ RetroSLICE</th>
<th>% Δ Mean $R^2_+\alpha$ RETROICOR</th>
<th>% Δ Mean $R^2_+\alpha$ RetroSLICE</th>
<th>% Δ Activation RETROICOR</th>
<th>% Δ Activation RetroSLICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB vs. none</td>
<td>-1.63</td>
<td>-4.06</td>
<td>2.87</td>
<td>48.28</td>
<td>56.82</td>
<td>49.27</td>
<td>-7.04</td>
<td>-9.81</td>
</tr>
<tr>
<td>PPG vs. none</td>
<td>-1.59</td>
<td>-1.27</td>
<td>-0.19</td>
<td>13.06</td>
<td>57.98</td>
<td>16.10</td>
<td>-0.36</td>
<td>-3.20</td>
</tr>
<tr>
<td>[RB + PPG] vs. none</td>
<td>-8.17</td>
<td>-5.41</td>
<td>44.08</td>
<td>57.08</td>
<td>227.32</td>
<td>64.97</td>
<td>-15.79</td>
<td>-18.65</td>
</tr>
</tbody>
</table>
Figure 4.1. Selected slices of the group average activation maps for the 1.5 T (A) and 3 T (B) datasets are shown without (top rows in each section) and with (bottom rows) physiologic noise correction applied. The colorbar shown to the upper right explains the Z-score scale for the overlay in these images. The center row of each section with the brain outline shows the type of correction responsible for any changes in the group activation maps when physiologic noise corrections were applied, according to the 7-color key shown to the bottom right. Gray shading in the center row indicates unchanged activation with noise correction.
CHAPTER 5

CONCLUSIONS

It was not long after the original development of functional MRI in the early 1990’s (Belliveau et al., 1991; Ogawa et al., 1992) that physiologic noise correction was recognized as a potentially important refinement to include in the data analysis (Hu et al., 1995; Biswal et al., 1996; Le and Hu, 1996). A glance through the bibliography reveals many research articles published since then, including several in the last few years, in which a novel physiologic noise correction algorithm was introduced or an existing technique was extended. Such studies generally include a comparison to previously published techniques using various metrics. However, when examining FMRI research at large, very few studies implement physiologic noise correction when the hypothesis is focused elsewhere.

Reasons for the lack of widespread adoption of physiologic noise correction are numerous. First, the implementation of any correction technique is not without difficulty and is often time-consuming, especially if results are to be calculated both with and without physiologic noise correction applied. Second, because prior publications without physiologic noise correction exist in almost every field, it may be unclear to what extent implementing physiologic noise correction would hinder comparisons with previous results. Additionally, there is a dearth of efficacy data for different noise correction
techniques applied to specific neuroimaging applications. For many researchers, this may lead to uncertainty over which algorithm is best to implement or may make the benefits of implementation unclear. Finally, there may be concern over invalidation of the results if a novel correction algorithm is applied incorrectly or subsequently found to be flawed.

This work attempted to better characterize different physiologic noise correction techniques applied to pain FMRI, with the goal of working towards defining the optimal physiologic noise correction algorithm to be used by future studies. Chapter 2 presented RetroSLICE, a novel FMRI physiologic noise correction algorithm. The cardiac and respiratory corrections are performed by direct linear regression, assuming an instantaneous effect on FMRI data from physiologic changes. The ETCO₂ correction implemented with RetroSLICE used the default hemodynamic response function to explain the relationship between ETCO₂ changes and MR signal changes, as was previously demonstrated (Wise et al., 2004). In this implementation at 1.5 T, the improvements in model fit with the inclusion of ETCO₂ correction exceeded those from cardiac and respiratory correction combined. Application of all three corrections improved the ability to determine brain activation (increased average model fit) by 129% and nearly every significant cluster of activation in the group activation map was affected by one or more of the physiologic noise corrections. This indicates that physiologic noise correction does influence the activation maps from which inferences are made about neuronal activity.

The novel ETCO₂ correction in RetroSLICE caused significant model fit improvements, even though it was applied with an assumed transfer function describing
the delay and shape of the MR signal response to a change in ETCO$_2$. The recent
deconvolution of a respiration response function that substantially differed from the
BOLD hemodynamic response function suggested that a similar procedure for ETCO$_2$
correction may optimize the results. With this goal in mind, an ETCO$_2$ transfer function
was empirically determined from BOLD data collected during a breathing modulation
experiment in chapter 3. Using optimized response functions for both, ETCO$_2$ was more
diffusely and strongly correlated to breathing modulation data than the RVT. This
indicates that RVT may not adequately approximate ETCO$_2$ when the breathing pattern is
uncoupled from arterial CO$_2$ levels.

In chapter 4, the most commonly used physiologic noise correction algorithm,
RETROICOR, was analyzed. The impact of correction was quantified for pain FMRI
data acquired at two field strengths, using similar metrics as in chapter 2. Baseline signal
noise was greater in data acquired at higher field, consistent with previous work (Kruger
et al., 2001). However, the reduction in signal noise with physiologic correction was also
greater at higher field. RETROICOR improved the average model fit by 227%,
significantly outperforming the equivalent respiratory and cardiac corrections in the
RetroSLICE algorithm, which improved model fit by only 65%. At the same time,
decreases in the statistical significance and extent of brain activation were seen with
RETROICOR. Using a higher physiologic data sampling rate and correcting for the
interleaved slice acquisition order showed no significant effect, which validates the
standard implementation of RETROICOR (Glover et al., 2000). In addition to
RETROICOR, ETCO$_2$ correction was employed using the optimized response function
determined in chapter 3. However, its impact on the summary statistics calculated was
secondary to that of combined respiratory and cardiac correction with RETROICOR and was surprisingly much less than with the non-optimized ETCO₂ correction described in chapter 2.

From these results we can conclude the following about physiologic noise correction in FMRI. First, the instantaneous effects of respiratory and cardiac fluctuations on the acquired FMRI data do not explain as much physiologic noise as a Fourier series generated from the respiratory and cardiac cycle phase values. Second, results for physiologic noise correction differ when compared across field strength. Thirdly, the RETROICOR algorithm seems to perform adequately well with physiologic data sampled at 40Hz and without correcting for slice acquisition times within an image volume. Finally, ETCO₂ correction may be warranted in certain FMRI applications, but further studies are needed to determine the best technique.
BIBLIOGRAPHY


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APPENDIX A

RESPIRATORY CHANGES IN RESPONSE TO PAINFUL ELECTRIC NERVE STIMULATION

Plot of respiratory rate (RR, shown in blue), tidal volume (TV, shown in red), and end-tidal carbon dioxide concentration (ETCO2, shown in black) changes that occur in response to repeated painful electric nerve stimulations. Taken with permission from (Ibinson 2004), in which it appears as figure 3.3c.
APPENDIX B

RETROSICLE PHYSIOLOGIC NOISE CORRECTION ALGORITHMS

% RetroSLICE physiologic noise correction algorithms by Keith Vogt
% A compilation of scripts: RB_correction.m & PPG_correction.m
%clear all; warning off MATLAB:divideByZero;
xdim = 64; ydim = 64; zdim = 28; %Matrix & slices
num_vol = 90; %vols per scan
alpha=0.05;
input='filtered'; %select between filtered and raw data

Results_matrix = zeros(1,12); %cols: 1=Subj, 2=blank, 3=Count,
%then [count, max. neg., max. pos.] in cols 4-6=RB, 7-9=PPG, & 10-12=PPG after RB
Results_counter = 0; %initialize row in Results_matrix
dir = strcat('E:\Data\ 1.5T_Pain\'); cd(dir);

subj_num_lookup = [1 2 3 5 6 7 8];%size(subj_num_lookup,2);
num_subjects = size(subj_num_lookup,2);
for subj_index = 1:num_subjects
subj = subj_num_lookup(subj_index);
subject_num = num2str(subj);
Results_counter = Results_counter + 1; %advance row in Results_matrix
Results_matrix(Results_counter,1) = subj; %write subj# to 1st col

% Filename construction
physio_data_file=strcat(dir,'\Subj',subject_num,'_PhysioData.mat');
CSV_filename = strcat(dir, 'Subj', subject_num, '_Dbl_correction.csv');
input_file = strcat(dir,'\feat_dirs\Subj',subject_num, scanID,'.feat\filtered_func_data.img'); %FMR images
RB_corrected_output_file = strcat('S',subject_num, scanID, '_RB_',input,'_corrected.img');
RB_correction_map_file = strcat('S',subject_num, scanID, '_RB_',input,'_correction_map.img');
PPG_output_file = strcat('S',subject_num, scanID, '_PPG_',input,'_corrected.img');
PPG_correction_map_file = strcat('S',subject_num, scanID, '_PPG_',input,'_correction_map.img');
RB_PPG_output_file = strcat('S',subject_num, scanID, '_RB_PPG_',input,'_corrected.img');
RB_PPG_correction_map_file = strcat('S',subject_num, scanID, '_RB_PPG_',input,'_correction_map.img');
save_file = strcat('S',subject_num, scanID, '_Dbl\',input,'_correction');

% load processed physio data from MATLAB data file, stored in RB_Amp & PPGUnit
load (physio_data_file, 'RB_Amp', 'PPGUnit');
%read in pre-processed MRI data
%NOTE: raw data is 'short' = 16-bit integer, but FSL filtered_func_data is 32-bit
%float', headers are always denoted with little-Endian
fid = fopen(input_file, 'rb'); %r for read, b for Big-Endian
data = fread(fid, [xdim * ydim * zdim * num_vol], 'float');
close(fid);
MR_data = reshape(data,xdim,ydim,zdim,num_vol);
clear data; %delete un-reshaped data

% Run RB correction
%Reorder Belt Amplitude data for Interleaved Acq
%RB_Amp is 'vol' rows by 'zdim' columns, read in from .mat physio_data file
j=1; %initialize
for inter=1:2:zdim
    BeltInterleaved(:,inter)=RB_Amp(1:num_vol,j);
    j=j+1;
end
for inter=2:2:zdim
    BeltInterleaved(:,inter)=RB_Amp(1:num_vol,j);
    j=j+1;
end

count=0;
res = zeros(xdim,ydim,zdim,num_vol);
RB_correctedimage = zeros(xdim,ydim,zdim,num_vol);
reg2 = zeros(xdim, ydim, zdim);
constants = zeros(xdim, ydim, zdim);
p = ones(xdim, ydim, zdim);
for imagez = 1:zdim
    for imagex = 1:xdim
        for imagey = 1:ydim
            avey = mean(MR_data(imagex,imagey,imagez,:)); %average through time
            if avey ~= 0
                array1 = MR_data(imagex,imagey,imagez,1:num_vol);
                Y1 = reshape(array1,1,num_vol);
                Y2 = Y1';
                X = BeltInterleaved(:,imagez);
                X2 = [X ones(num_vol,1)];
                [B,BINT,RINT,STATS] = regress(Y2,X2,alpha); %linear regression to find betas
                reg2(imagex,imagey,imagez) = B(1);  %unthresholded correction map
                constants(imagex,imagey,imagez) = B(2);
                res(imagex,imagey,imagez,:) = R;
                p(imagex,imagey,imagez) = STATS(3);
                RB_correctedimage(imagex,imagey,imagez,:) = R + B(2);
                count = count+1;
            end
        end
    end
end

%write corrected multi-vol image file
fid = fopen(RB_corrected_output_file,'wb');
fwrite(fid, RB_correctedimage,'float'); %have to write out as float
fclose(fid);
clear RB_correctedimage;

%Threshold p image, making mask
p2 = 1.-p;
for zz = 1:zdim
    p2thresh_Amp(:,:,zz) = im2bw(p2(:,:,zz),.95);
end
clear p2;

%Write correction quantification for RB for Results_matrix
Results_matrix(Results_counter,3) = count; %total voxels in the brain
Results_matrix(Results_counter,4) = sum(sum(sum(p2thresh_Amp))); %# of sig voxels w/ RB

%write correction map as an image
RB_correction_map = reg2.*p2thresh_Amp; %makes map of correlated voxels for Amp
fid = fopen(RB_correction_map_file,'wb');
fwrite(fid,RB_correction_map,'short'); %have to write map as short
fclose(fid);
clear p2thresh_Amp;

Results_matrix(Results_counter,5) = min(min(min(RB_correction_map)));
Results_matrix(Results_counter,6) = max(max(max(RB_correction_map)));% Run PPG correction %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Loop for moving values into array with interleaving
j=1; %initialization
for inter=1:2:zdim %odd slices
    PPGInterleaved(:,inter)=PPGUnit(1:num_vol,j);
    j=j+1;
end
for inter=2:2:zdim %even slices
    PPGInterleaved(:,inter)=PPGUnit(1:num_vol,j);
    j=j+1;
end

count=0;
res = zeros(xdim,ydim,zdim,num_vol);
PPG_corrected_image = zeros(xdim,ydim,zdim,num_vol);
reg2 = zeros(xdim, ydim, zdim);
constants = zeros(xdim, ydim, zdim);
p = ones(xdim, ydim, zdim);
for imagez = 1:zdim
    for imagex = 1:xdim
        for imagey = 1:ydim
            avey = mean(MR_data(imagex,imagey,imagez,:));
            if avey ~= 0
                array1 = MR_data(imagex,imagey,imagez,1:num_vol);
                Y1 = reshape(array1,1,num_vol);
                Y2 = Y1';
                X = PPGInterleaved(:,imagez);
                X2 = [X ones(num_vol,1)];
                [B,BINT,R,RINT,STATS] = regress(Y2,X2,alpha); %linear regression to find betas
                reg2(imagex,imagey,imagez) = B(1); %unthresholded correction map
                constants(imagex,imagey,imagez) = B(2);
                res(imagex,imagey,imagez,:,:) = R;
                p(imagex,imagey,imagez) = STATS(3);
                PPG_corrected_image(imagex,imagey,imagez,:) = R + B(2);
                count = count+1;
            end
        end
    end
end

%write corrected image
fid = fopen(PPG_output_file,'wb');
fwrite(fid,PPG_corrected_image,'float'); %output file must be float, big-Endian,
fclose(fid);
clear PPG_corrected_image; %clear the huge image file
clear MR_data;
%Threshold p image
p2 = 1.-p;
for zz=1:zdim
   p2thresh(:,:,zz) = im2bw(p2(:,:,zz),.95);
end
Results_matrix(Results_counter,7) = sum(sum(sum(p2thresh))); %# of sig voxels

%write correction map as an image
PPG_correction_map = reg2 .* p2thresh; %makes map of correlated voxels
fid = fopen(PPG_correction_map_file,'wb');
fwrite(fid,PPG_correction_map,'short'); %map but be written as short
fclose(fid);

Results_matrix(Results_counter,8) = min(min(min(PPG_correction_map)));
Results_matrix(Results_counter,9) = max(max(max(PPG_correction_map)));

% Run PPG on RB_corrected data
fid = fopen(RB_corrected_output_file, 'rb'); % r for read, b for Big-Endian
data = fread(fid, [xdim * ydim * zdim * num_vol], 'float');
close(fid);
RB_corrected_image = reshape(data,xdim,ydim,zdim,num_vol);
clear data; %delete un-reshaped data

count=0;
res = zeros(xdim,ydim,zdim,num_vol);
RB_PPG_corrected_image = zeros(xdim,ydim,zdim,num_vol);
reg2 = zeros(xdim, ydim, zdim);
constants = zeros(xdim, ydim, zdim);
p = ones(xdim, ydim, zdim);
for imagez = 1:zdim
   for imagex = 1:xdim
      for imagey = 1:ydim
         avey = mean(RB_corrected_image(imagex,imagey,imagez,:));
         if avey ~= 0
            array1 = RB_corrected_image(imagex,imagey,imagez,:);
            Y1 = reshape(array1,1,num_vol);
            Y2 = Y1';
            X = PPGInterleaved(:,imagez);
            X2 = [X ones(num_vol,1)];
            [B,BINT,R,RINT,STATS] = regress(Y2,X2,alpha); %linear regression to find betas
            reg2(imagex,imagey,imagez) = B(1); %unthresholded correction map
            constants(imagex,imagey,imagez) = B(2);
            res(imagex,imagey,imagez,:) = R;
            p(imagex,imagey,imagez) = STATS(3);
            RB_PPG_corrected_image(imagex,imagey,imagez,:) = R + B(2);
            count = count+1;
         end
      end
   end
end

%write corrected image;
fid = fopen(RB_PPG_output_file,'wb');
fwrite(fid,RB_PPG_corrected_image,'float'); %output file must be float, big-Endian,
close(fid);
clear *_corrected_image; %clear both huge image files

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clear res;

%Threshold p image
p2 = 1.-p;
for zz=1:zdim
    p2thresh(:,:,zz) = im2bw(p2(:,:,zz),.95);
end

%Results_matrix(1,3)=count; %display total voxels in the brain
Results_matrix(Results_counter,10) = sum(sum(sum(p2thresh))); %# of sig voxels

%write correction map as an image
RB_PPG_correction_map = reg2 .* p2thresh; %makes map of correlated voxels
fid = fopen(RB_PPG_correction_map_file,'wb');
fwrite(fid,RB_PPG_correction_map,'short'); %map but be written as short
fclose(fid);

Results_matrix(Results_counter,11)=min(min(min(RB_PPG_correction_map)));
Results_matrix(Results_counter,12)=max(max(max(RB_PPG_correction_map)));

save (save_file); %write Matlab variables to disk
end %ends big FOR loop for subject

csvwrite(CSV_filename, Results_matrix); %write to csv file
APPENDIX C

PHYSIOLOGIC DATA PARSING ALGORITHMS

%Physiologic Data Parsing Algorithms - Keith Vogt
% The Ohio State University
%A representative compilation of portions of the following scripts:
% PhysioParse_BM_500Hz_RET.m - created 12/16/08
% PhysioParse_RL_500Hz_RET.m - created 6/24/08
% No_delay_CO2cRF_BM.m - created 1/14/09
% No_delay_RVTcRRF_BM.m - created 1/14/09
%Input: Subj*_wavedata.txt= BIOPAC data in text file w/ columns= time(min), RB, PPG, ETCO2, & Trigger
%Variables: Timing_by_vol= Array variable with of TR starts (sample numbers)
% ETCO2_peaks= Array of ETCO2 peak info (3 cols= actual sample#, sample# + sampling_delay, peak Amp)
% ETCO2_interpolated= Array of 1 ETCO2 value per vol interpolated to TR start
% RVT_interp_by_vol= Array of RVT values interpolated to each TR start
% RET_data= PPG & RB data formatted for RETROICOR script
%Outputs: Subj#_ETCO2_interpolated.txt= value of ETCO2 interpolated to begining of ea. TR interval
% Subj#_RVT_by_vol.txt= value of RVT interpolated to beginning of ea. TR interval
% Subj#_500Hz_RET_data.txt= PPG & RB data formatted for RETROICOR script
% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
%Constants for experimental setup
num_slices = 35; num_vol = 210; %FMRI dataset dimensions
trigger_thres = 9; %threshold for trigger peak, in Volts
V_thres_ETCO2 = 4.5; %threshold for peak ETCO2, in Volts
ETCO2_pct_change_thresh = -20; %allow 20% decrease between consecutive CO2 peaks
CO2_transit_delay = 4100; %delay = 8.2s * 500Hz; In terms of number of samples
sampling_rate = 500; %samples per second (Hz)
TR = 3; %TR interval in seconds
qtr_sec = sampling_rate/4; half_sec = sampling_rate/2;
one_sec = sampling_rate; %redundant, but simplifies understanding in Boolean expressions later
TR_samples = TR * sampling_rate; %number of samples in TR interval
samples_per_slice = 43; % Slice spacing is TR/#_slices * 500Hz

subj_num_lookup = [1 2 4 5 6 7 8 9]; %array with subj#s to process
num_subjects = size(subj_num_lookup,2);
for subj_index = 1:num_subjects
    subj = subj_num_lookup(subj_index); %find subj# in array
    subject_num = num2str(subj); %subject ID as string
%Construct I/O filenames
    input_filename = strcat(dir, 'Subj',subject_num,'_BM_wavedata.txt');
    ETCO2_interpolated_filename = strcat('Subj',subject_num,'_ETCO2_interpolated.txt');
    RVT_filename = strcat('Subj',subject_num,'_RVT_by_vol.txt');
    RET_physio_filename = strcat('Subj',subject_num,'_BM_500Hz_RET_data.txt');

%Dimension variables
    ETCO2_by_vol = ones(num_vol,1);
    Timing_by_vol = zeros(num_vol,1);
    Physio_by_slice = zeros(num_vol * num_slices,5);
no_CO2_peak_volumes = zeros(10,3); no_CO2_peak_counter = 0;

%Read in physiologic data from BIOPAC that is stored in text file
% (rows = sample#) with five columns: time(min), Resp Belt, PPG, ETCO2, & Trigger
wavedata = load(input_filename); % default should be -ascii, since ext is not *.mat

% Pre-loop initialization
num_samples = size(wavedata, 1); %find number of samples in data set
physio_slice_index = 1; %index for physio values for each slice
found_ETCO2_peak_flag = 0; disp_flag = 0;
vol_index = 1; current_sample = 1; %sample numbers in loop

%%%Main wavedata parse loop, finds sample number for each TR start and ETCO2 value for each vol
while current_sample < num_samples
    if wavedata(current_sample, 5) < trigger_thresh %no peak in trigger if col 5 < set Voltage
        current_sample = current_sample + 1; %no trigger peak, so increment & repeat
    else %we have a peak on the trigger channel
        TR_start = current_sample; %save value of begining sample for vol
        for x = 1:num_slices %write times (min) & wave values to array for ea slice in vol
            Physio_by_slice(physio_slice_index,:) = wavedata(current_sample,1:5);
            physio_slice_index = physio_slice_index + 1;
        end %ends FOR loop
        current_sample = current_sample + samples_per_slice;
        look_back=1; %initialize, num samples to go backwards in physio data
        while found_ETCO2_peak_flag==0 %don't have peak yet, need to go backwards in physio data
            if (wavedata(TR_start + CO2_transit_delay - look_back - one_sec:TR_start + CO2_transit_delay - look_back + one_sec, 4) > V_thres_ETCO2)
                %found a peak, so save into array
                ETCO2_by_vol(vol_index,1) = wavedata(TR_start + CO2_transit_delay - look_back, 4); %ETCO2 value for this volume
                Timing_by_vol(vol_index,2) = TR_start + CO2_transit_delay - look_back; %ETCO2 peak (prev)
                Timing_by_vol(vol_index,3) = ETCO2_by_vol(vol_index); %ETCO2 value for this volume
                prev_ETCO2=wavedata(TR_start + CO2_transit_delay - look_back, 4);
                vol_index=vol_index+1; %increment counter for ETCO2 array
                found_ETCO2_peak_flag=1; %change flag value
                break %end for loop to save time
            end
        end %ends skip_ahead FOR loop
    end %ends TR_for loop
 end %ends TR_for loop
%Loops to find ETCO2 peaks corresponding to each volume
%ETCO2 calc by vol based on peak in curve - 1sec window, if present or previous peak
if (TR_start + CO2_transit_delay + TR_samples + sampling_rate + 2) < num_samples %check for end of data
    for skip_ahead = CO2_transit_delay :(CO2_transit_delay + TR_samples)
        %search for peak in expired CO2 waveform in block corresponding to current TR
        if (wavedata(TR_start+skip_ahead,4) == max(wavedata(TR_start + skip_ahead-one_sec:TR_start+skip_ahead+one_sec,4)))
            %found a peak, so save into array
            ETCO2_by_vol(vol_index,1) = wavedata(TR_start+skip_ahead,4); %ETCO2 value for this volume
            Timing_by_vol(vol_index,2) = TR_start + skip_ahead; %ETCO2 peak (prev)
            Timing_by_vol(vol_index,3) = ETCO2_by_vol(vol_index); %ETCO2 value for this volume
            prev_ETCO2=wavedata(TR_start+skip_ahead,4);
            vol_index=vol_index+1; %increment counter for ETCO2 array
            found_ETCO2_peak_flag=1; %change flag value
            break %end for loop to save time
        end
    end %ends FOR loop
end %ends TR_for loop

% have peak from previous TR
no_CO2_peak_counter = no_CO2_peak_counter + 1;
ETCO2_by_vol(vol_index,1) = wavedata(TR_start + CO2_transit_delay - look_back, 4); %ETCO2 value for this volume
Timing_by_vol(vol_index,2) = TR_start; %Sample number of TR start for vol
Timing_by_vol(vol_index,3) = ETCO2_by_vol(vol_index); %ETCO2 value

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%write location and value of vols with no TR to array
no_CO2_peak_volumes(no_CO2_peak_counter, 1) = vol_index; %vol number
no_CO2_peak_volumes(no_CO2_peak_counter, 2) = TR_start; %sample # of vol begin
no_CO2_peak_volumes(no_CO2_peak_counter, 3) = ETCO2_by_vol(vol_index); %ETCO2 value
vol_index = vol_index + 1;
found_ETCO2_peak_flag = 1; %change flag value, stop looking for prev peak
end %ends IF looking for peak
look_back = look_back + 1; %go further back to find peak
end %ends while loop looking back for peak ETCO2
found_ETCO2_peak_flag=0; %set flag back to zero

else % we have run out of data when looking ahead for ETCO2, display error message
disp('CO2 recording ended prematurely. Remember delay!');
end %ends IF-ELSE checking for EOF in wavedata for CO2 calc
end %ends IF-ELSE for trigger peak
end %ends while loop for all samples in wavedata
if physio_slice_index < 40
disp('No peaks detected in trigger channel!!');
end

%%% Find all ETCO2 peaks in physiol. data recording
ETCO2_peaks = ones(100, 3); %new variable for all ETCO2 peak values (cols= actual sample#, sample# +
sampling_delay, peak Amp)
ETCO2_peak_index = 1; current_sample = (one_sec + CO2_transit_delay + 1);
while current_sample < (num_samples - (one_sec + 1)) %loop through most all samples
%Check for ETCO2 peak on Chan 4 (max in 2s window and > threshold)
if wavedata(current_sample, 4) == max(wavedata(current_sample - one_sec : current_sample + one_sec, 4)) &&
wavedata(current_sample, 4) > V_thres_ETCO2

%Peak ahead to check for matching peak further along, advance if found
if wavedata(current_sample + 1, 4) == max(wavedata(current_sample - one_sec : current_sample + one_sec, 4))
current_sample = current_sample + 1;
else
break; %exit current WHILE loop if no subsequent volume
end
end %ends WHILE checking for max in wavedata
%current_sample = current_sample - 1; %previous loop goes 1sampel past end of peak plateau, adjust here
%Found a peak, so save into array
if ETCO2_peak_index > 1
if current_sample - ETCO2_peaks(ETCO2_peak_index - 1, 1) > one_sec;
ETCO2_peaks(ETCO2_peak_index, 1) = current_sample; %location of peak
ETCO2_peaks(ETCO2_peak_index, 2) = current_sample - CO2_transit_delay; %location of actual end-
expiration
ETCO2_peaks(ETCO2_peak_index, 3) = wavedata(current_sample, 4); %peak (end-tidal) CO2 value
ETCO2_peak_index = ETCO2_peak_index + 1; %increment counter for ETCO2 array
else %overwrite previous value
ETCO2_peaks(ETCO2_peak_index - 1, 1) = current_sample; %location of peak
ETCO2_peaks(ETCO2_peak_index - 1, 2) = current_sample - CO2_transit_delay; %location of actual end-
expiration
ETCO2_peaks(ETCO2_peak_index - 1, 3) = wavedata(current_sample, 4); %peak (end-tidal) CO2 value
end %IF checking for first ETCO2_peak_index value
end %ends WHILE searching for ETCO2 peaks
else %special case (though same code) for first row in peak array
ETCO2_peaks(ETCO2_peak_index, 1) = current_sample; %location of peak
ETCO2_peaks(ETCO2_peak_index, 2) = current_sample - CO2_transit_delay; %location of actual end-
expiration
ETCO2_peaks(ETCO2_peak_index, 3) = wavedata(current_sample, 4); %peak (end-tidal) CO2 value
ETCO2_peak_index = ETCO2_peak_index + 1; %increment counter for ETCO2 array
end

end %ends IF checking for first ETCO2_peak_index value

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end\%IF checking for max in wavedata
  current_sample = current_sample + 1; \%increment sample number
end\%WHILE loop

%%% Check ETCO2_by_vol for incomplete breaths on CO2 tracing
num_CO2_peaks = size(ETCO2_peaks, 1);
for breath_index = 2 : num_CO2_peaks \%re-use counter variable
  prev_ETCO2 = ETCO2_peaks(breath_index - 1, 3); \%3rd col has ETCO2 Amp
  current_ETCO2 = ETCO2_peaks(breath_index, 3);
  pct_change_CO2 = 100*(current_ETCO2 - prev_ETCO2) / prev_ETCO2;
  if pct_change_CO2 < ETCO2_pct_change_thresh \%then we have > 20\% drop in ETCO2 with current breath
    \%Disp msg and look for better value fwd
    disp(strcat('Note:_', num2str(pct_change_CO2),'\% change in ETCO2 for peak#',num2str(breath_index),' at sample#',num2str(ETCO2_peaks(breath_index, 1))));
  end %IF-
  if (breath_index+1 <= num_CO2_peaks) && 100*(ETCO2_peaks(breath_index+1, 3) - prev_ETCO2) / prev_ETCO2 >= ETCO2_pct_change_thresh - 5 \%more liberal range for immediate next peaks
    ETCO2_peaks(breath_index, 3) = (ETCO2_peaks(breath_index+1, 3) + prev_ETCO2) / 2; \%average two values in ETCO2_peaks
    disp(strcat(num2str(current_ETCO2),' replaced with_', num2str(ETCO2_peaks(breath_index, 3)), ', average of prev=', num2str(prev_ETCO2),'& next-1=', num2str(ETCO2_peaks(breath_index+1, 3))));
  elseif (breath_index+2 <= num_CO2_peaks) && 100*(ETCO2_peaks(breath_index+2, 3) - prev_ETCO2) / prev_ETCO2 >= ETCO2_pct_change_thresh
    ETCO2_peaks(breath_index, 3) = (ETCO2_peaks(breath_index+2, 3) + prev_ETCO2) / 2; \%average two values in ETCO2_peaks
    disp(strcat(num2str(current_ETCO2),' replaced with_', num2str(ETCO2_peaks(breath_index, 3)), ', average of prev=', num2str(prev_ETCO2),'& next-2=', num2str(ETCO2_peaks(breath_index+2, 3))));
  elseif (breath_index+3 <= num_CO2_peaks) && 100*(ETCO2_peaks(breath_index+3, 3) - prev_ETCO2) / prev_ETCO2 >= ETCO2_pct_change_thresh
    ETCO2_peaks(breath_index, 3) = (ETCO2_peaks(breath_index+3, 3) + prev_ETCO2) / 2; \%average two values in ETCO2_peaks
    disp(strcat(num2str(current_ETCO2),' replaced with_', num2str(ETCO2_peaks(breath_index, 3)), ', average of prev=', num2str(prev_ETCO2),'& next-3=', num2str(ETCO2_peaks(breath_index+3, 3))));
  else disp('New trend detected, no change made.');
  end %ELSE-THEN
end %FOR loop for ETCO2_peaks parse
ETCO2_delayed = ETCO2_peaks(:, 2:3); \%copy cols 2&3; gas sampling delay accounted for in ETCO2_delayed

% Add timing information of dummy volumes for delay shifting later
Timing_by_pre_vol = zeros(10,1); \%array for 10 dummy volumes preceeding image acquisition
first_TR_start = Timing_by_vol(1,1);
for vol = 1:10 \%work backwards to create artificial TR start points
  Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
end
Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)]; \%concat into single vector

%%% Interpolate shifted ETCO2 values to begining of ea. TR
ETCO2_interpolated = zeros(num_vol, 1); \%variable for interpolated ETCO2 values
look_back = 1; \%initialze
for vol_index = 1 : num_vol+10 \%Loop to find prev and current CO2 peak amplitude and timing for ea. TR
  TR_start = Timing_expanded(vol_index, 1);
  while ETCO2_delayed(peak_index, 1) < TR_start \%advance peak_index past current TR start (may be > 1 with ea. vol advance)
    peak_index = peak_index + 1;
  end
  \%Interpolate from prev ETCO2 to TR start using current value
  ETCO2_prev = ETCO2_delayed(peak_index, 1); \%ETCO2 Amp stored in col 2
  ETCO2_current = ETCO2_delayed(peak_index, 2); \%peak_index points to value past TR start
  \%Add timing information of dummy volumes for delay shifting later
  Timing_by_pre_vol = zeros(10,1); \%array for 10 dummy volumes preceeding image acquisition
  first_TR_start = Timing_by_vol(1,1);
  for vol = 1:10 \%work backwards to create artificial TR start points
    Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
  end
  Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)]; \%concat into single vector

  \%Add timing information of dummy volumes for delay shifting later
  Timing_by_pre_vol = zeros(10,1); \%array for 10 dummy volumes preceeding image acquisition
  first_TR_start = Timing_by_vol(1,1);
  for vol = 1:10 \%work backwards to create artificial TR start points
    Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
  end
  Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)]; \%concat into single vector

  \%Add timing information of dummy volumes for delay shifting later
  Timing_by_pre_vol = zeros(10,1); \%array for 10 dummy volumes preceeding image acquisition
  first_TR_start = Timing_by_vol(1,1);
  for vol = 1:10 \%work backwards to create artificial TR start points
    Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
  end
  Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)]; \%concat into single vector
samp_prev = ETCO2_delayed(peak_index - 1, 1); %gas sampling delay already accounted for in col 1 of ETCO2_delayed
samp_current = ETCO2_delayed(peak_index, 1); ETCO2_interpolated(vol_index) = ETCO2_prev + (TR_start - samp_prev)*(ETCO2_current - ETCO2_prev)/(samp_current - samp_prev);
end%FOR loop for vol, advance to next TR start (+1 vol)
save (ETCO2_interpolated_filename, 'ETCO2_interpolated', '-ASCII');

%%% Calculate RVT values from RB timecourse
% Engineered from description in (Birn et al. 2008 NIMG v40 p644)
% Method: Interpolate max, min, and period first, then calculate RVT
% First find peaks & troughs in RB timecourse
RB_peak_index = 1; %initialize loop counter (equivalent to breath number index)
RB_peaks_and_troughs = zeros(100,4);  %Re-initialize array for pos and negative RB peaks, overwriting prev values
%  cols:1=pos peak samp#, 2=peak (max) Amp, 3=following trough samp#, 4=trough (min) Amp
current_sample = one_sec + 1; %reinitialize sample number to near begining of data acquisition (want to find all peaks)
% Find pos. peaks and store timing + Amp in first two cols of RB_peaks_and_troughs
while current_sample < (num_samples - (one_sec + 1)) && current_sample < (Timing_by_vol(num_vol+vols_expand,1) + 2*TR_samples) %check for end of data
%Find max in col 2 (Chan 1) of wavedata using 2-second window; in terms of samples this allows max RR of 30/min
if wavedata(current_sample, 2) == max(wavedata(current_sample - one_sec : current_sample + one_sec, 2)) &&
wavedata(current_sample, 2) == wavedata(current_sample - one_sec : current_sample + one_sec, 2)
%then we have UNIQUE peak; col 2 in Physio_by_slice is RB (take timing to be beginning of peak/trough)
RB_peaks_and_troughs(RB_peak_index, 1) = current_sample; %col1 = pos peak samp# (beginning)
RB_peaks_and_troughs(RB_peak_index, 2) = wavedata(current_sample, 2); %col2 = peak Amp
%Find subsequent trough in RB timecourse
while current_sample < (num_samples - (one_sec + 1)) && current_sample < (Timing_by_vol(num_vol + vols_expand,1) + 2.5*TR_samples) %check for end of data
if wavedata(current_sample, 2) == min(wavedata(current_sample - one_sec : current_sample + one_sec, 2)) &&
wavedata(current_sample, 2) == wavedata(current_sample - one_sec : current_sample + one_sec, 2)
%then we have UNIQUE trough; col 2 in Physio_by_slice is RB
RB_peaks_and_troughs(RB_peak_index, 3) = current_sample; %col3 = trough samp# (beginning)
RB_peaks_and_troughs(RB_peak_index, 4) = wavedata(current_sample, 2); %col4 = trough Amp
break; %exit trough-finding (innermost) WHILE loop only
end%IF, trough
current_sample = current_sample + 1; %next min not found, next sample in inner WHILE loop
end%WHILE for trough
RB_peak_index = RB_peak_index + 1; %advance
end%IF for max
current_sample = current_sample + 1; %if next max not found, try next sample in outer WHILE loop
end%ends outer while loop for RB peak/trough find
delay = 0 * one_sec; %Delay, in number of samples, would be inserted here

num_RB_peaks = size(RB_peaks_and_troughs,1); %num of rows in peak/trough matrix
RB_peaks_and_troughs_delayed = zeros(num_RB_peaks, 4); %initialize array
RB_peaks_and_troughs_delayed(:,1) = RB_peaks_and_troughs(:, 1) + delay; %copy peak times shifted by delay
RB_peaks_and_troughs_delayed(:,2) = RB_peaks_and_troughs(:, 2); %copy peak amplitude unchanged
RB_peaks_and_troughs_delayed(:,3) = RB_peaks_and_troughs(:, 3) + delay; %copy trough times shifted by delay
RB_peaks_and_troughs_delayed(:,4) = RB_peaks_and_troughs(:, 4); %copy trough amplitude unchanged

Timing_by_pre_vol = zeros(10,1); %array for 10 dummy volumes preceeding image acquisition
first_TR_start = Timing_by_vol(1,1);
for vol = 1:10 %work backwards to create 10 artificial TR start points
  Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
end
Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)]; %concat into single vector

%%% Interpolate respiratory peak, trough, and period values to beginning of each TR interval
Peak_trough_period_interp = zeros(num_vol + 10, 5); %dim 5 col new matrix
resp_period_current = 0; resp_period_prev = 0; breath_index = 1; %initialize variables
current_trough_flag = 0; %set flag indicating current trough params still need calculated

if RB_peaks_and_troughs_delayed(1,3) < Timing_by_vol(1,1) %Then, have a trough before first TR start to interpolate from
for vol_index = 1 : (num_vol + 10)
  if vol_index == 115; break; end
  % For each vol (including 10 preceding dummy vols), calculate interpolated peak and trough values
  TR_start = Timing_expanded(vol_index, 1);
  %Find last peak value before current TR start
  while RB_peaks_and_troughs_delayed(breath_index, 1) < TR_start
    %sample# for breath before TR start; store values (possibly too early, so advance with loop)
    peak_Amp_prev = RB_peaks_and_troughs_delayed(breath_index, 2); %store prev peak value
    peak_samp_prev = RB_peaks_and_troughs_delayed(breath_index, 1);
    if RB_peaks_and_troughs_delayed(breath_index, 3) < TR_start %is trough also before?
      trough_Amp_prev = RB_peaks_and_troughs_delayed(breath_index, 4); %store prev trough value
      trough_samp_prev = RB_peaks_and_troughs_delayed(breath_index, 3);
      current_trough_flag = 0; %current trough params still need calculated
    elseif breath_index > 1 %make sure not outside array limits (trough occurs after TR_start due to logic of 1st IF)
      trough_Amp_prev = RB_peaks_and_troughs_delayed(breath_index - 1, 4); %store prev trough value
      trough_samp_prev = RB_peaks_and_troughs_delayed(breath_index - 1, 3);
      current_trough_flag = 1; %current trough params calculated below
    end%IF
    breath_index = breath_index + 1;
  end%WHILE
  % Set current peak amplitude and sample #, and calc current resp period
  peak_Amp_current = RB_peaks_and_troughs_delayed(breath_index, 2); %amplitude of peak past TR start
  peak_samp_current = RB_peaks_and_troughs_delayed(breath_index, 1);
  resp_period_current = peak_samp_current - peak_samp_prev; % Calculate respiratory period
  if current_trough_flag == 0 %current trough params still need calculated
    trough_Amp_current = RB_peaks_and_troughs_delayed(breath_index, 4);
    trough_samp_current = RB_peaks_and_troughs_delayed(breath_index, 3);
  end
  current_trough_flag = 0; %rest flag value for next loop

  Peak_trough_period_interp(vol_index, 1) = peak_Amp_prev + (TR_start - peak_samp_prev)*(peak_Amp_current - peak_Amp_prev)/(peak_samp_current - peak_samp_prev);
  Peak_trough_period_interp(vol_index, 2) = trough_Amp_prev + (TR_start - trough_samp_prev)*(trough_Amp_current - trough_Amp_prev)/(trough_samp_current - trough_samp_prev);
  Peak_trough_period_interp(vol_index, 3) = resp_period_prev + (TR_start - peak_samp_prev)*(resp_period_current - resp_period_prev)/(peak_samp_current - peak_samp_prev);
  Peak_trough_period_interp(vol_index, 4) = TR_start; % TR_start in actual wavedata in col4
  Peak_trough_period_interp(vol_index, 5) = breath_index; % breath_index in col5
end%WHILE

% Find last peak value before current TR start
% For each vol (including 10 preceding dummy vols), calculate interpolated peak and trough values
%if RB_peaks_and_troughs_delayed(breath_index, 1) < TR_start
%  %sample# for breath before TR start; store values (possibly too early, so advance with loop)
%  peak_Amp_prev = RB_peaks_and_troughs_delayed(breath_index, 2); %store prev peak value
%  peak_samp_prev = RB_peaks_and_troughs_delayed(breath_index, 1);
%  if RB_peaks_and_troughs_delayed(breath_index, 3) < TR_start %is trough also before?
%    trough_Amp_prev = RB_peaks_and_troughs_delayed(breath_index, 4); %store prev trough value
%    trough_samp_prev = RB_peaks_and_troughs_delayed(breath_index, 3);
%    current_trough_flag = 0; %current trough params still need calculated
%  elseif breath_index > 1 %make sure not outside array limits (trough occurs after TR_start due to logic of 1st IF)
%    trough_Amp_prev = RB_peaks_and_troughs_delayed(breath_index - 1, 4); %store prev trough value
%    trough_samp_prev = RB_peaks_and_troughs_delayed(breath_index - 1, 3);
%    current_trough_flag = 1; %current trough params calculated below
%  end%IF
%  breath_index = breath_index + 1;
%  if breath_index > 3 %check for array limit error, should have advanced past 3rd breath before 1st TR start
%    peak_samp_minus_two = RB_peaks_and_troughs_delayed(breath_index - 2, 1); %sample # two peaks back
%    %peak_samp_prev = RB_peaks_and_troughs_delayed(breath_index - 1, 1); %sample # of prev peak
%    resp_period_prev = peak_samp_minus_two - peak_samp_prev;
%  end%WHILE
%  % Set current peak amplitude and sample #, and calc current resp period
%  peak_Amp_current = RB_peaks_and_troughs_delayed(breath_index, 2); %amplitude of peak past TR start
%  peak_samp_current = RB_peaks_and_troughs_delayed(breath_index, 1);
%  resp_period_current = peak_samp_current - peak_samp_prev; % Calculate respiratory period
%  if current_trough_flag == 0 %current trough params still need calculated
%    trough_Amp_current = RB_peaks_and_troughs_delayed(breath_index, 4);
%    trough_samp_current = RB_peaks_and_troughs_delayed(breath_index, 3);
%  end
%  current_trough_flag = 0; %rest flag value for next loop
%  Peak_trough_period_interp(breath_index, 1) = peak_Amp_prev + (TR_start - peak_samp_prev)*(peak_Amp_current - peak_Amp_prev)/(peak_samp_current - peak_samp_prev);
%  Peak_trough_period_interp(breath_index, 2) = trough_Amp_prev + (TR_start - trough_samp_prev)*(trough_Amp_current - trough_Amp_prev)/(trough_samp_current - trough_samp_prev);
%  Peak_trough_period_interp(breath_index, 3) = resp_period_prev + (TR_start - peak_samp_prev)*(resp_period_current - resp_period_prev)/(peak_samp_current - peak_samp_prev);
%  Peak_trough_period_interp(breath_index, 4) = TR_start; % TR_start in actual wavedata in col4
%  Peak_trough_period_interp(breath_index, 5) = breath_index; % breath_index in col5
end%WHILE
%% Copy current values to prev & advance to calc new "current" values
peak_Amp_prev = peak_Amp_current;
peak_samp_prev = peak_samp_current;
trough_Amp_prev = trough_Amp_current;
trough_samp_prev = trough_samp_current;
resp_period_prev = resp_period_current;
breath_index = breath_index - 1;
end
%FOR loop through all vols
else disp('Major Error: First value in Timing_by_vol not preceeded by value in RB_peaks_and_troughs_delayed');
end
%IF checking for no breath prior to first TR start

%%%% Calculate RVT from interpolated peak, trough & period values
RVT_interp_by_vol = zeros(num_vol + 10, 1); %array to hold RVT values
% RVT = Amp(peak - trough) / period (sample_peak - sample_peak_prev); scaled by x1k to make values easier to work with
for vol_num = 1 : (num_vol+10) %loop through all volumes and 10 extra
RVT_interp_by_vol(vol_num) = 1000*(Peak_trough_period_interp(vol_num, 1) - Peak_trough_period_interp(vol_num, 2)) / Peak_trough_period_interp(vol_num, 3);
end
save (RVT_filename, 'RVT_interp_by_vol', '-ASCII');

% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
%Create RETROICOR regressors
RET_data_points = (num_vol)* TR *sampling_rate; %just an estimate for now
Resampled_wavedata = zeros(RET_data_points, 3); %matrix to hold resampled PPG & RB values
resamp_counter = 1; %initialize at beginning of new array
%current_sample = first_TR_start; %start at stored value of 1st trig peak
for vol_num = 1 : num_vol %loop through all TR intervals
current_sample = Timing_by_vol(vol_num,1);
for resamp_loop = 1:floor(sampling_rate*TR/2) %doing two data points at once due to rounding, so loop half the number of new samples per TR
Resampled_wavedata(resamp_counter, 1) = wavedata(current_sample, 3); %PPG
Resampled_wavedata(resamp_counter, 2) = wavedata(current_sample, 2); %RB
Resampled_wavedata(resamp_counter, 3) = current_sample; %for manual verification w/ Acknowledge
current_sample = current_sample + floor(sampling_rate/sampling_rate); %increment by 12 samples
resamp_counter = resamp_counter + 1; %increment
Resampled_wavedata(resamp_counter, 1) = wavedata(current_sample, 3); %PPG
Resampled_wavedata(resamp_counter, 2) = wavedata(current_sample, 2); %RB
Resampled_wavedata(resamp_counter, 3) = current_sample; %for manual verification w/ Acknowledge
current_sample = current_sample + ceil(sampling_rate/sampling_rate); %increment by 13 samples
resamp_counter = resamp_counter + 1; %increment
end
%FOR loop for resampling each TR
end
% Second loop to find PPG peaks and replace with -1000 flag value
RET_qtr_sec = round(sampling_rate/4); %
RET_data = zeros(RET_data_points, 2); %initialize
resamp_counter = 2; %need to initialize
while resamp_counter < RET_data_points %use +/- qtr-second window below for max HR of < 120bpm
if resamp_counter < (RET_qtr_sec + 1)
if Resampled_wavedata(resamp_counter,1) == max(Resampled_wavedata(1 : RET_qtr_sec, 1)) &&
Resampled_wavedata(resamp_counter, 1) == Resampled_wavedata(resamp_counter - 1, 1)
%window modified for first qtr sec of data
RET_data(resamp_counter, 1) = -1000; %write value -1k to mark location of PPG peak
RET_PPG_data(resamp_counter) = -1000;
end
elseif resamp_counter > (RET_data_points - (RET_qtr_sec))
if Resampled_wavedata(resamp_counter,1) == max(Resampled_wavedata(resamp_counter - RET_qtr_sec : RET_data_points, 1)) &&
Resampled_wavedata(resamp_counter, 1) == Resampled_wavedata(resamp_counter - 1, 1)
end
120
%Window modified for within last qtr_sec of data
RET_data(resamp_counter, 1) = -1000; %write value -1k to mark location of PPG peak
RET_PPG_data(resamp_counter) = -1000;
end

elseif resamp_counter <= (RET_data_points - RET_qtr_sec)
    if Resampled_wavedata(resamp_counter, 1) == max(Resampled_wavedata(resamp_counter - RET_qtr_sec : resamp_counter + RET_qtr_sec, 1)) && Resampled_wavedata(resamp_counter, 1) ~= Resampled_wavedata(resamp_counter - 1, 1)
        %Then we have UNIQUE peak (or 1st occurrence of peak value) in 1/2 sec window
        RET_data(resamp_counter, 1) = -1000; %write value -1k to mark location of PPG peak
        RET_PPG_data(resamp_counter) = -1000;
    end
end
resamp_counter = resamp_counter + 1;
end %ends while loop for PPG peak calc

RET_data(:,2) = round(5000*Resampled_wavedata(1:RET_data_points,2) + 5000); %Re-scale and round RB Amp values and copy to col2

%Write output files and loop to next subject
save (RET_physio_filename, 'RET_data', '-ASCII'); %write RET physio data to txt file
end%FOR loop for subject
APPENDIX D

ETCO₂ RESPONSE FUNCTION REGRESSION ALGORITHMS

%%ETCO₂ response function regression algorithms - Keith Vogt
%% The Ohio State University
%% A representative compilation of the following scripts:
%% No_delay_CO2cRF_BM.m - created 1/14/09
%% Multi_delay_CO2_BM.m - created 12/8/08
%% Matlab_CO2_correction_RL.m - created 2/4/09
%% No_delay_stat_map_summary.m - created 1/18/09

%% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
xdim = 64;  ydim = 64;  num_slices = 35;  num_vol = 210; % Image dimensions
%Dimension matrices and initialize
Subj_avg_stats = zeros(num_subjects, 8); %Summary stats for all subjects
%Cols: 1=subj#, 2=count, 3=F_max, 4=F_avg, 5=R2_max, 6=R2_avg, 7=p_min, 8=p_mean
Subj_avg_stats(:,7) = ones (num_subjects,1); %init min p col to value of one

%%% Create Response function kernel, using fn. from FMRIstat package
PEAK1= 12; FWHM1= 7; PEAK2= 26; FWHM2= 9; RATIO= 0.7;
HRF_parameters = [PEAK1 FWHM1 PEAK2 FWHM2 RATIO];
time = (0:800)/10; %define time axis (0 to 80 sec)
HRF_cache = fmridesign(time, 0, [1 0], [], HRF_parameters); %call FMRIstat script
HRF = HRF_cache.X(:,1,1); %copy relevant dim of data structure to variable 'HRF'

% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
%%%%% Algorithm for CO2 regression with no time shifting
%Inputs: HRF created above
%   ETCO2_interpolated= Array variable, 1 ETCO2 value/vol interpolated to TR start
%   Subj#_BM_filtered_interleaved_500Hz_RET.nii= RETROICOR-corrected MR dataset
%Variable: Subj_avg_stats - see description with initialization above
%Outputs: Subj#_BM_no_delay_ETCO2c*.txt= convolved ETCO2 timecourse as text file (1 value/vol)
%   Subj#_BM_no_delay_ETCO2c*_[Beta, F_stat, R2, p_value]_map.nii= maps of respective regression stats
%   No_delay_stat_summary*.csv= Excel file with all-subj regression summary statistics
%   Subj#_scanID_Matlab_CO2_corrected.nii= ETCO2 corrected MR data
%Approximate runtime = 1.5 hours / 8 subjects
analysis_tag = strcat('_no_delay_ETCO2c',num2str(PEAK1),'-',num2str(FWHM1),'-',num2str(PEAK2),'-',num2str(FWHM2),'-pt',num2str(RATIO*10));
CSV_filename = strcat(dir, 'No_delay_stat_summary', analysis_tag, '.csv'); %Output file, all-subj summary stats
for subj_index = 1 : num_subjects %loop through all subjects
  subj = subj_num_lookup(subj_index);
  subject_num = num2str(subj); %subject ID as string
  %Construct subject-specific filenames
  MR_filename = strcat(dir, 'Subj',subject_num,'_BM_filtered_interleaved_500Hz_RET.nii');
  %...
ETCO2_convolved_filename = strcat(dir, 'No_delay data\Subj',subject_num,'_BM', analysis_tag ,'.txt');
outdir = strcat(dir, 'No_delay maps\'); %change directories for output maps
ETCO2_Beta_map_filename = strcat(outdir, 'Subj',subject_num,'_BM', analysis_tag ,'_Beta_map.nii');
ETCO2_F_stat_map_filename = strcat(outdir, 'Subj',subject_num,'_BM', analysis_tag ,'_F_stat_map.nii');
ETCO2_R2_map_filename = strcat(outdir, 'Subj',subject_num,'_BM', analysis_tag ,'_R2_map.nii');
ETCO2_p_value_map_filename = strcat(outdir, 'Subj',subject_num,'_BM', analysis_tag ,'_p_value_map.nii');
Corrected_file = strcat(dir, 'Subj',subject_num, 'b\Subj', subject_num, short_tag, analysis_tag, '.nii');

% Read in stored variables from PhysioParse.m run and data
data_struct = fmris_read_nifti(MR_filename); %Read NIFTI format image data
MR_4D_data = reshape(data_struct.data, xdim, ydim, num_slices, num_vol);
data_struct = fmris_read_nifti(strcat(dir, 'example_func.nii')); %use this template for writing later

% Dim new variables
ETCO2_Beta_map = zeros(xdim, ydim, num_slices); %map for regression coefficients
ETCO2_F_stat_map = zeros(xdim, ydim, num_slices); %map for F-score of regression
ETCO2_R2_map = zeros(xdim, ydim, num_slices); %map for model fit
ETCO2_p_value_map = ones(xdim, ydim, num_slices); %init p-matrix to 1, since low value = good
Corrected_data = zeros(xdim, ydim, num_slices, short_vols); % ETCO2-corrected data

% Convolve interpolated ETCO2 timecourse with response function (gamma as default)
test_counter = 1;
% Add 30 interpolated values between each ETCO2 value to "increase" temporal resolution of ETCO2 timecourse
% so it is in the same time frame as the response function (10 values/sec)
for vol = 1:num_vol
    inc = (ETCO2_interpolated(vol+1) - ETCO2_interpolated(vol)) / 30; %increment between values
    for sub_TR  = 1:30
        ETCO2_test(test_counter) = ETCO2_interpolated(vol) + sub_TR*inc;
        test_counter = test_counter + 1;
    end
end
ETCO2_test = ETCO2_test - ETCO2_test(size(ETCO2_test,2)); %shift waveform so it ends at zero
ETCO2_convolved = conv(ETCO2_test, HRF);  %CONVOLUTION - order of inputs do NOT matter

%Downsample shifted + convolved waveform to 1 value per volume (3s)
ETCO2_convolved_by_vol = zeros(num_vol,1);
TR_count = 1;
for hi_res_counter = 301:30:6600 %skip 1st 30s of data (dummy volumes) added previously for shifting
    ETCO2_convolved_by_vol(TR_count) = ETCO2_convolved (hi_res_counter);
    TR_count = TR_count + 1;
end

%Write convolved ETCO2 timecourse as text file (for FSL input)
save (ETCO2_convolved_filename, 'ETCO2_convolved_by_vol', '-ASCII');

%%%% Regress CO2 against filtered MR data, check for best value (this delay?), and store
ETCO2_X = [ETCO2_convolved_by_vol ones(num_vol,1)]; %add col of ones for regression
for z = 1:num_slices %loop through MR data
for y = 1:ydim
    if mean(voxel_timeseries) ~= 0 %in brain?
        % Regress convolved & delayed ETCO2 against MR timecourse
        [Beta, Beta_95pct_CI, Residuals, Res_95pct_CI, Stats] = regress(voxel_timeseries, ETCO2_X);
        ETCO2_Beta_map(x,y,z) = Beta(1); %Beta(2) is constant term
        ETCO2_F_stat_map(x, y, z) = Stats(1);
        ETCO2_R2_map(x, y, z) = Stats(2);
        ETCO2_p_value_map(x, y, z) = Stats(3); %unthresholded p-value map
        end%IF for in brain (non-zero timeseries)
    end%x loop
end%y loop
end%slice loop

%%% Write 3D stat matrices as image files
data_struct.file_name = ETCO2_Beta_map_filename;
data_struct.data = ETCO2_Beta_map(:,:,:);
fmris_write_nifti(data_struct);
data_struct.file_name = ETCO2_F_stat_map_filename;
data_struct.data = ETCO2_F_stat_map(:,:,:);
fmris_write_nifti(data_struct);
data_struct.file_name = ETCO2_R2_map_filename;
data_struct.data = ETCO2_R2_map(:,:,:);
fmris_write_nifti(data_struct);
data_struct.file_name = ETCO2_p_value_map_filename;
data_struct.data = ETCO2_p_value_map(:,:,:);
fmris_write_nifti(data_struct);

%%% Calculate summary statistics over subject's brain
Subj_avg_stats(subj_index, 1) = subj;   %write subject numbers to array col 1
%Loop through all voxels, determine if in brain, & write stats
count = 0;
for x = 1:xdim
  for y = 1:ydim
    for z = 1:num_slices
      if F_stat_map(x,y,z) ~= 0 && p_value_map(x,y,z) < 0.05  %in brain and significant?
        count = count + 1; %Counter variable for number of significant voxels
        % Write subj summary values (temporarily write running total values to summary matrix for means)
        if Subj_avg_stats(subj_index, 3) < F_stat_map(x,y,z); Subj_avg_stats(subj_index, 3) = F_stat_map(x,y,z);
        end %max_F
        Subj_avg_stats(subj_index, 4) = Subj_avg_stats(subj_index, 4) + F_stat_map(x,y,z);  %total F
        if Subj_avg_stats(subj_index, 5) < R_squared_map(x,y,z); Subj_avg_stats(subj_index, 5) =
        R_squared_map(x,y,z); end %max_R2
        Subj_avg_stats(subj_index, 6) = Subj_avg_stats(subj_index, 6) + R_squared_map(x,y,z); %total R2
        if Subj_avg_stats(subj_index, 7) > p_value_map(x,y,z); Subj_avg_stats(subj_index, 7) =
        p_value_map(x,y,z); end %min_p
        Subj_avg_stats(subj_index, 8) = Subj_avg_stats(subj_index, 8) + p_value_map(x,y,z);  %total_p
        end%IF
      end%IF for in brain (non-zero timeseries)
    end%FOR loop for z
  end%FOR loop for y
end%FOR loop for x
Subj_avg_stats(subj_index, 2) = count;
%Divide running totals by in-brain count to store average
Subj_avg_stats(subj_index, 4) = Subj_avg_stats(subj_index, 4) / count;
Subj_avg_stats(subj_index, 6) = Subj_avg_stats(subj_index, 6) / count;
Subj_avg_stats(subj_index, 8) = Subj_avg_stats(subj_index, 8) / count;
csvwrite(CSV_filename, Subj_avg_stats); % Write results matrices to comma separated value files

%%% Perform CO2 correction on each voxel; regress, subtract correlated portion, and store
ETCO2_X = [ETCO2_convolved_by_vol ones(short_vols,1)]; %add col of ones for regression
for z = 1:num_slices %loop through MR data
  for y = 1:ydim
    for x = 1:xdim
      voxel_timeseries = reshape(MR_4D_data(x, y, z, :short_vols), short_vols, 1); %store as 1D array
      if mean(voxel_timeseries) ~= 0 %in brain?
        % Regress convolved ETCO2 data against MR timecourse
        [Beta, Beta_95pct_CI, Residuals, Res_95pct_CI, Stats] = regress(voxel_timeseries, ETCO2_X);
        % Subtract correlated portion Beta*X and store "corrected" result
        Corrected_data(x, y, z, :) = Residuals + Beta(2);  %C + r = Y - BX
        end%IF for in brain (non-zero timeseries)
    end%FOR loop for x
  end%FOR loop for y
end%FOR loop for x
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end loop

end slice loop

%%% Write best fit by delay matrices to image files
data_struct.file_name = Corrected_file;
data_struct.data = Corrected_data;
fmris_write_nifti(data_struct);

end loop for Subj in no_delay analysis

%%% Algorithm for CO2 regression with multiple delay times
%Inputs: HRF created above
% ETCO2_peaks= Array variable containing ETCO2 peak timing information
% Subj#_BM_filtered_interleaved_500Hz_RET.nii= RETROICOR-corrected MR dataset, as above
%Variable: delay= array containing delay times to use for shifting
%Outputs: Subj#_BM_no_delay_ETCO2c* [Delay, F_stat, R2, p_value]_map.nii= maps of best stats over all delays
% Stat_by_delay*.csv= large data table with fits at each delay value
% Avg_delay_stats*.csv= average values over all delay times (summary table)
%Approximate runtime = 3 hours / subject

analysis_tag = strcat('_ETCO2c',num2str(PEAK1),'-',num2str(FWHM1),'-',num2str(PEAK2),'-',num2str(FWHM2),'-',
delay, num2str(DIP*10));
big_CSV_filename = strcat(dir, 'Stat_by_delay', analysis_tag, '.csv');
avg_CSV_filename = strcat(dir, 'Avg_delay_stats', analysis_tag, '.csv');

for subj_index = 1 : num_subjects %loop through all subjects
    subj = subj_num_lookup(subj_index);
    subject_num = num2str(subj);  %subject ID as string
    %Construct filenames
    ETCO2_delay_map_filename = strcat(dir, 'Subj',subject_num,'_BM', analysis_tag,'_delay_map.nii');
    ETCO2_F_stat_map_filename = strcat(dir, 'Subj',subject_num,'_BM', analysis_tag,'_F_stat_map.nii');
    ETCO2_R2_map_filename = strcat(dir, 'Subj',subject_num,'_BM', analysis_tag,'_R2_map.nii');
    ETCO2_p_value_map_filename = strcat(dir, 'Subj',subject_num,'_BM', analysis_tag,'_p_value_map.nii');

    %Dim new variables
    ETCO2_delay_map = zeros(xdim, ydim, num_slices) - 9; %cannot use 0 for default here since 0 sec delay is valid
    ETCO2_F_stat_map = zeros(xdim, ydim, num_slices);
    ETCO2_R2_map = zeros(xdim, ydim, num_slices); %maps for best regression values
    ETCO2_p_value_map = ones(xdim, ydim, num_slices); %init p-matrix to 1, since low value = good

%%% Add delay to ETCO2 timing in ETCO2_peaks variable
    for delay = -4*one_sec : half_sec : 16*one_sec  %40 time shifts for CO2; 'delay' is in number of samples
        delay_sec = delay / sampling_rate;
        ETCO2_delayed = ETCO2_peaks(:, 2:3);  %copy cols 2&3; accounts for gas sampling delay in ETCO2_delayed
        ETCO2_delayed(:,1) = ETCO2_delayed(:, 1) + delay; %shift sample numbers in col 1 by delay term

        Timing_by_pre_vol = zeros(10,1); %array for 10 dummy volumes preceeding image acquisition
        Timing_by_pre_vol(1,1) = Timing_by_vol(1,1);
        for vol = 1:10 %array backwards to create artificial TR start points
            Timing_by_pre_vol(vol) = first_TR_start - (10-vol)*TR_samples;
        end
        Timing_expanded = [Timing_by_pre_vol; Timing_by_vol(:,1)';]; %concat into single vector

        %%% Interpolate shifted ETCO2 values to beginning of ea. TR
        look_back = 1; %initialize
        for vol_index = 1 : num_vol + 10  %Loop to find prev and current CO2 peak amplitude and timing for ea. TR
            Timing_by_pre_vol(vol_index) = first_TR_start - (10-vol)*TR_samples;
        end
    end
end

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TR_start = Timing_expanded(vol_index, 1);
while ETCO2_delayed(peak_index, 1) < TR_start %advance peak_index until past current TR start (may be > 1 with ea. TR advance)
    peak_index = peak_index + 1;
end
%Interpolate from prev ETCO2 to TR start using current value
ETCO2_prev = ETCO2_delayed(peak_index - 1, 2); %ETCO2 Amp stored in col 2
ETCO2_current = ETCO2_delayed(peak_index, 2); %peak_index points to value past TR start
samp_prev = ETCO2_delayed(peak_index - 1, 1); %gas sampling delay already accounted for in col 1 of ETCO2_delayed
samp_current = ETCO2_delayed(peak_index, 1);
ETCO2_interpolated(vol_index) = ETCO2_prev + (TR_start - samp_prev)*(ETCO2_current - ETCO2_prev)/(samp_current - samp_prev);
end %FOR loop for vol, advance to next TR start (+1 vol)

%%% Convolve interpolated ETCO2 timecourse with response function (gamma as default)
test_counter = 1;
% Add 30 interpolated values between each ETCO2 value to "increase" temporal resolution of ETCO2 timecourse
% so it is in the same time frame as the response functions (10 values/sec)
for vol = 1:num_vol
    inc = (ETCO2_interpolated(vol+1) - ETCO2_interpolated(vol)) / 30; %increment between
    for sub_TR  = 1:30
        ETCO2_test(test_counter) = ETCO2_interpolated(vol) + sub_TR*inc;
        test_counter = test_counter + 1;
    end
end
ETCO2_test = ETCO2_test - ETCO2_test(size(ETCO2_test,2)); %shift waveform so it ends at zero
ETCO2_convolved = conv(ETCO2_test, HRF); %CONVOLUTION - order of inputs do NOT matter

%Downsample shifted + convolved waveform to 1 value per volume
ETCO2_convolved_by_vol = zeros(num_vol,1);
TR_count = 1;
for hi_res_counter = 301:30:6600 %skip 1st 30s of data (dummy volumes) added previously for shifting
    ETCO2_convolved_by_vol(TR_count) = ETCO2_convolved(hi_res_counter);
    TR_count = TR_count + 1;
end

%%% Regress CO2 against filtered MR data, check for best value (this delay?), and store
ETCO2_X = [ETCO2_convolved_by_vol  ones(num_vol,1)]; %add col of ones for regression
for z = 1:num_slices %loop through MR data
    for y = 1:ydim
        for x = 1:xdim
            voxel_timeseries = reshape(MR_4D_data(x, y, z, 1:num_vol), 210, 1); %store as 1D array
            if mean(voxel_timeseries) ~=0 %in brain?
                % Regress convolved & delayed ETCO2 against MR timecourse
                [Beta, Beta_95pct_CI, Residuals, Res_95pct_CI, Stats] = regress(voxel_timeseries, ETCO2_X);
                if Stats(2) > ETCO2_F_stat_map(x, y, z) %does F_stat exceed stored value
                    ETCO2_R2_map(x, y, z) = Stats(1);
                    ETCO2_F_stat_map(x, y, z) = Stats(2);
                    ETCO2_p_value_map(x, y, z) = Stats(3); %unthresholded p-value map
                    ETCO2_delay_map(x, y, z) = delay / sampling_rate; %store the delay (in sec) that yielded these stats
                    end
                end
            end
        end%x loop
    end%y loop
end%slice loop
end%FOR loop for ETCO2 delay shifting

%%% Write best fit by delay matrices to image files

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data_struct.file_name = ETCO2_delay_map_filename;
data_struct.data = ETCO2_delay_map(:,:,);
fmrisc_write_nifti(data_struct);
data_struct.file_name = ETCO2_F_stat_map_filename;
data_struct.data = ETCO2_F_stat_map(:,:,);
fmrisc_write_nifti(data_struct);
data_struct.file_name = ETCO2_R2_map_filename;
data_struct.data = ETCO2_R2_map(:,:,);
fmrisc_write_nifti(data_struct);
data_struct.file_name = ETCO2_p_value_map_filename;
data_struct.data = ETCO2_p_value_map(:,:,);
fmrisc_write_nifti(data_struct);

%%% Calculate summary statistics over subject's brain
Subj_avg_stats(subj_index, 1) = subj;  %Write subject number to array col 1
count = 0; %initialize
for x = 1:xdim  %Loop through all voxels, determine if in brain, & write stats
  for y = 1:ydim
    for z = 1:num_slices
      if F_stat_map(x,y,z) ~= 0 && p_value_map(x,y,z) < 0.05  %in brain and significant?
        count = count + 1;
        %write subj summary values (temporarily write running total values to summary matrix for means)
        Subj_avg_stats(subj_index, 2) = Subj_avg_stats(subj_index, 2) + Delay_map(x,y,z);  %total delay
        if Subj_avg_stats(subj_index, 3) < F_stat_map(x,y,z); Subj_avg_stats(subj_index, 3) = F_stat_map(x,y,z);
        end %max_F
        Subj_avg_stats(subj_index, 4) = Subj_avg_stats(subj_index, 4) + F_stat_map(x,y,z);  %total F
        if Subj_avg_stats(subj_index, 5) < R_squared_map(x,y,z); Subj_avg_stats(subj_index, 5) = R_squared_map(x,y,z);
        end %max_R2
        Subj_avg_stats(subj_index, 6) = Subj_avg_stats(subj_index, 6) + R_squared_map(x,y,z);  %total R2
        if Subj_avg_stats(subj_index, 7) > p_value_map(x,y,z); Subj_avg_stats(subj_index, 7) = p_value_map(x,y,z);
        end %min_p
        Subj_avg_stats(subj_index, 8) = Subj_avg_stats(subj_index, 8) + p_value_map(x,y,z);  %total_p
      end
      %write summary values for each delay
      delay_index = 0;
      for delay_time = delay_start : delay_increment : delay_stop
        delay_index = delay_index + 1;
        Stat_by_delay((subj_index - 1)*(num_delay_times) + delay_index, 1) = subj;
        if Delay_map(x,y,z) == delay_time
          Stat_by_delay((subj_index - 1)*(num_delay_times) + delay_index, 3) = Stat_by_delay((subj_index-1)*(num_delay_times) + delay_index, 3) + 1;  %increment count
        end
      end
    end
  end
end

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Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 8) = p_value_map(x,y,z);
end%IF
Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 9) = Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 9) + p_value_map(x,y,z), %total p
end%IF
end%FOR loop for delay time
end%IF
end%FOR loop for z
end%FOR loop for y
end%FOR loop for x

% Divide running totals by in-brain count to store average
Subj_avg_stats(subj_index, 2) = Subj_avg_stats(subj_index, 2) / count;
Subj_avg_stats(subj_index, 4) = Subj_avg_stats(subj_index, 4) / count;
Subj_avg_stats(subj_index, 6) = Subj_avg_stats(subj_index, 6) / count;
Subj_avg_stats(subj_index, 8) = Subj_avg_stats(subj_index, 8) / count;

% Divide running totals in Stat_by_delay by count value col 3
delay_index = 0;
for delay_time = delay_start : delay_increment : delay_stop
    delay_index = delay_index + 1;
    Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 5) = Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 5) / Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 3);
Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 7) = Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 7) / Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 3);
Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 9) = Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 9) / Stat_by_delay(((subj_index - 1)*(num_delay_times) + delay_index, 3);
end%small FOR loop for delay time

% Write summary value matrices as Excel files
csvwrite(big_CSV_filename, Stat_by_delay);
end%FOR loop for subject
APPENDIX E

NOISE CORRECTION SUMMARY STATISTIC CALCULATIONS

% Noise Correction summary statistic calculations
% Keith Vogt 3/15/2009
% The Ohio State University
% An example for 3T including scripts: All_param_calc.m & Noise_calc.m
% Reads in filtered_func_data, res4d, and thresh_zstat files from feat directory and calculates:
% signal noise, voxel count, Ra2, & Zstat values for each subject and saves in maps
% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
% Constants for experimental setup (3T shown as example)
xdim = 64; ydim = 64; num_slices = 35; num_vol = 90; % dimensions
dir = strcat('N:\_FMRI\Keith\3T Pain RL - 2\');
% % % % % % % % % % % % % % % % % % % % % % % % % % % % % % % %
% Calculate Ra2, Z-score, and voxel count
input = '_filtered_interleaved_500Hz';
CSV_filename = '3T Pain RL-interleaved_500Hz_RET.csv'; % file for summary values from all subjects

subj_num_lookup = [1 5 8 17 20 21];
num_subjects = size(subj_num_lookup,2);
Results_counter = 0; % initialize row in Results_matrix
Results_matrix = zeros(num_subjects * 4, 11); % Matrix to store summary values for each dataset, written to spreadsheet at end
% Cols: 1 = Subj# 2 = Scan_ID, 3 = correction_ID (see key below), 4 = p, 5 = in-brain_cnt, 6 = max_Ra2, 7 = mean_Ra2,
% 8 = std_dev(Ra2), 9 = active_voxel_cnt, 10 = max_Zstat, 11 = max_Tstat
for subj_index = 1 : num_subjects
    subj = subj_num_lookup(subj_index);
    subject_num = num2str(subj); % subject ID as string
    cd(dir); % change directory
    for scan = 1:2
        if scan == 1; scanID = '_4R1'; end
        if scan == 2
            scanID = '_4R2'; % set scan ID tag
        end
        if subj == 8 || subj == 20
            break; % exit loop for scan _4R2 for these subjects due to motion
        end
    end %if for scan

    for correction = 1:5
        % correction ID: 1 = pain_only, 2 = RB, 3 = PPG, 4 = RB + PPG, 5 = RET + ETCO2
        correctionID = ['_' correction ID ' '];
        Results_counter = Results_counter + 1; % advance row in Results_matrix
        if correction == 1; p = 1; correctionID = '_pain_only'; end
        if correction == 2; p = 2; correctionID = '_RB'; end
        if correction == 3; p = 2; correctionID = '_PPG'; end
        if correction == 4; p = 3; correctionID = '_RB_PPG'; end
        if correction == 5; p = 4; correctionID = '_RET_ETCO2'; end

end % for correction

end % for subj_index
end % for scan
end % for subj_index
end % for scan
if correction == 5; p = 4; correctionID = '_RET_ETCO2'; end
Results_matrix(Results_counter,1) = subj; %write subj# to 1st col
Results_matrix(Results_counter,2) = scan;
Results_matrix(Results_counter,3) = correction;
Results_matrix(Results_counter,4) = p; %num of parameters

common_feat_string = strcat(dir,'feat_dirs_FSL4pt1\Subj',subject_num, scanID);
common_output_string = strcat(dir,'Subj',subject_num,'\Subj',subject_num, scanID, input, correctionID);

%Set I/O file names - DO NOT change from original filtered_func from pain only analysis
input_data_filename = strcat(common_feat_string,'\_filtered_interleaved.feat\filtered_func_data.nii');

switch correction
    case 1 %pain only
        feat_dir = strcat(common_feat_string, '_filtered_interleaved.feat');
    case 2 %RB
        feat_dir = strcat(common_feat_string, input, '_RET_RB.feat');
    case 3 %PPG
        feat_dir = strcat(common_feat_string, input, '_RET_PPG.feat');
    case 4 %Both RB & PPG
        feat_dir = strcat(common_feat_string, input, '_RET.feat');
    case 5 %RET + ETCO2
        feat_tag = strcat(common_feat_string, input, '_Matlab_CO2_corrected.feat');
end

input_res_filename = strcat(feat_dir, '\stats\res4d.nii');
Ra2_filename = strcat(common_output_string, '_Ra2_map.nii');
input_Zstat_filename = strcat(feat_dir, '\thresh_zstat1.nii');
input_Tstat_filename = strcat(feat_dir, '\stats\stat1.nii');
save_filename = strcat(common_output_string,'_Ra2_data.mat');

%Read in data matrices
Filtered_struct = fmris_read_nifti(input_data_filename);
Filtered_data_4D = reshape(Filtered_struct.data, xdim, ydim, num_slices, num_vol);
Res_struct = fmris_read_nifti(input_res_filename);
Res_data_4D = reshape(Res_struct.data, xdim, ydim, num_slices, num_vol);
Zstat_struct = fmris_read_nifti(input_Zstat_filename);
Zstat_data_3D = reshape(Zstat_struct.data, xdim, ydim, num_slices);
Results_matrix(Results_counter, 10) = max(max(max(Zstat_data_3D)));
Tstat_struct = fmris_read_nifti(input_Tstat_filename);
Tstat_data_3D = reshape(Tstat_struct.data, xdim, ydim, num_slices);
Results_matrix(Results_counter, 11) = max(max(max(Tstat_data_3D)));
clear Tstat_data_3D;
	n = num_vol; %number of vols = num of timepoints
Ra2_count = 0; %Number of non-zero voxels in Ra2 maps
active_voxel_count = 0; %Number of non-zero voxels in activation maps

for x = 1:xdim
    for y = 1:ydim
        for z = 1:num_slices
            %Ra2 calculations
            avey = mean(Filtered_data_4D(x, y, z, :));
            if avey ~= 0
                for t=1:num_vol
                    sse = (Res_data_4D(x,y,z,t))^2 + sse;
                    sst = (Filtered_data_4D(x,y,z,t) - avey)^2 + sst;
                end
                if sse ~= 0
                    Ra2 = 1-((sse/(n-p))/(sst/(n-1)));
                end
            end
        end
    end
end

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if isfinite(Ra2)
    Ra2Image(x,y,z) = Ra2;
    Ra2_count = Ra2_count+1;
end
else %outside of brain
    Ra2Image(x,y,z) = 0;
end
%Parse thresh _Zstat image
if Zstat_data_3D(x,y,z) ~= 0
    active_voxel_count = active_voxel_count + 1;
end
end %slice loop
end%ydim
end%xdim
%calc averages, used below
mean_Ra2 = (sum(sum(sum(Ra2Image))))/ Ra2_count;
%Update results matrix for this scan
Results_matrix(Results_counter, 5) = Ra2_count; %should be count of in-brain voxels
Results_matrix(Results_counter, 9) = active_voxel_count;
Results_matrix(Results_counter, 6) = max(max(max(Ra2Image))); %max_Ra2
Results_matrix(Results_counter, 7) = mean_Ra2;

%Standard Deviation calculations for Ra2 and activation maps
SumSq_Ra2 = 0;  % running totals of (Xi-avg)^2 values through Ra2 and Zstat matrices
for x = 1:xdim %loop through image space in 3 dimensions again
    for y = 1:ydim
        for z = 1:num_slices
            if Ra2Image(x,y,z)~=0
                SumSq_Ra2 = (Ra2Image(x,y,z) - mean_Ra2)^2 + SumSq_Ra2;
            end%IF
        end %slice loop
    end%y
end%x
Results_matrix(Results_counter, 8) = (SumSq_Ra2 / Ra2_count)^0.5;  %Standard deviation of Ra2 value
%Stan error of mean can then be calculated manually by dividing by sqrt of the number of datasets
% Write Ra2 map as NIFTI file
Ra2_map_struct = Zstat_struct;
Ra2_map_struct.file_name = Ra2_filename;
Ra2_map_struct.data = Ra2Image;
fmrnis_write_nifti(Ra2_map_struct);
end %correction loop (change corrections)
end %scan loop (i.e. change subjects & repeat)
end %subj loop (i.e. change subjects & repeat)
csvwrite(CSV_filename, Results_matrix);  %write to csv file
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correctionID = '_interleaved_5000Hz_RB';
feat_tag = '_500Hz RET RB.feat';
case 3 %PPG
    correctionID = '_interleaved_5000Hz_PPG';
    feat_tag = '_500Hz RET_PPG.feat';
case 4 %Both RB & PPG
    correctionID = '_interleaved_5000Hz_RB_PPG';
    feat_tag = '_500Hz RET.feat';
case 5 %RET + ETCO2
    correctionID = '_interleaved_5000Hz_RET_ETCO2';
    feat_tag = 'Matlab_CO2_corrected.feat';
end

CSV_filename = strcat(dir, 'All_subj_3T_RL', correctionID, '_temp_std_dev.csv');

for subj_loop = 1 : num_subjects
    subj = subj_num_lookup(subj_loop);
    subject_num = num2str(subj);  %subject ID as string
    for scan = 1:2
        if scan == 1; scanID = '_4R1';  end
        if scan == 2
            scanID ='_4R2';  %set scan ID tag
            if subj == 8 || subj == 20
                break;  %exit loop for scan _4R2 for these subjects due to motion
            end
        end%IF for scan7
        results_counter = results_counter + 1;  %increment col for new scan
        %Construct filenames
        feat_dir = strcat(dir, 'feat_dirs_FSL4pt1\Subj', subject_num, scanID, feat_tag);
        input_data_filename = strcat(feat_dir, '\filtered_func_data.nii');  %use FMRIstat script to read in NIFTI data
        Filtered_struct = fmris_read_nifti(input_data_filename);
        Filtered_data_4D = reshape(Filtered_struct.data, xdim, ydim, num_slices, num_vol);
        %loop through all voxels & calc mean in time dimension
        for t = 1:num_vol %for each timepoint
            for slice = 1:num_slices  %find avg & std for each slice
                count_in_slice = 0;  slice_total = 0;  mean_slice = 0;
                for x = 1:xdim
                    for y = 1:ydim
                        if Filtered_data_4D(x,y,slice,1) ~= 0  %not outside brain
                            count_in_slice = count_in_slice + 1;
                            slice_total = slice_total + Filtered_data_4D(x,y,slice,t);
                        end%if
                    end
                end
                mean_slice = slice_total / count_in_slice;  %Calc mean signal for ea. slice
                mean_results(t, slice, results_counter, 1) = mean_slice;  %Write to mean_results matrix
            end%FOR loop for slice
        end%FOR loop for scanID
end FOR loop for subject

%Write one CSV file (table) for all subjects in each type of correction

csvwrite(CSV_filename, std_dev_results);
end FOR loop for correction