A Filtered Subtraction Approach for the Reduction of Physiological Noise in Perfusion Based fMRI

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Introduction

Physiological noise is a dominant source of noise in fMRI experiments, especially at higher field strengths. A previous study showed that the sensitivity of perfusion based fMRI could be significantly improved by removing physiological noise components from the tag and control images separately, using a modified version of a image based retrospective correction method (RETROICOR) [1,2]. However, this method was not directly comparable to the filtered subtraction schemes typically employed in the analysis of ASL data. In this work, we present a new model in which physiological noise is removed from the perfusion time series obtained from the filtered subtraction of the tag and control images. We then compare the statistical performance of the filtered approach to the previous unfiltered approach by using experimental data obtained from functional ASL studies of the visual cortex and hippocampal region.

Theory

In an arterial spin labeling (ASL) experiment, a series of control images and tag images in which arterial blood is either fully relaxed or magnetically inverted, respectively, is acquired. Typically, the control and tag images are acquired in an interleaved fashion and a perfusion time series is formed from the filtered subtraction of the images. By adding physiological noise terms for tag and control images [2] to the ASL signal model described in [3], the ASL data can be described in matrix form as:

$$\mathbf{y} = s_m M_0 \mathbf{b} + s_q \mathbf{q} \circ \mathbf{b} + \alpha \exp(-TI/T_{1B})\mathbf{M}(\mathbf{q} \circ \mathbf{b}) + \mathbf{U}_c\mathbf{D}_c\mathbf{P}\mathbf{c}_c + \mathbf{U}_t\mathbf{D}_t\mathbf{P}\mathbf{c}_t + \mathbf{e}$$

where **y** is ASL time series consisting of interleaved tag and control images, **b** represents multiplicative BOLD weighting**, q** represents perfusion, **e** is an additive noise term, **M** is a *NxN* diagonal matrix consisting of alternating –1 and 1s along the diagonal, and $\mathbf{q} \circ \mathbf{b}$ denotes the Hadamard product of two vectors (i.e. element-by-element multiplication). The terms s_m, s_q, α, *TI,* and T_{1B} denote pulse sequence dependent terms and relaxation constants. Physiological noise terms are $\mathbf{U}_c\mathbf{D}_c\mathbf{P}\mathbf{c}_c + \mathbf{U}_t\mathbf{D}_t\mathbf{P}\mathbf{c}_t$ where **P** is a *Nxm* matrix containing *m* physiological regressors and $\mathbf{c}_c$ and $\mathbf{c}_t$ are unknown regressor weights for the control and tag images, respectively. The calculation of these regressors follows the approach presented in [1] for the RETROICOR method. The term $\mathbf{U}_c\mathbf{D}_c\mathbf{P}\mathbf{c}_c$ represents physiological noise contributions to the control images where $\mathbf{D}_c$ is a downsampling matrix that picks out every odd sample of $\mathbf{P}\mathbf{c}_c$ and $\mathbf{U}_c$ is an upsampling matrix that inserts zeros between samples of $\mathbf{D}_c\mathbf{P}\mathbf{c}_c$. The matrices $\mathbf{U}_t$ and $\mathbf{D}_t$ are defined similarly, with $\mathbf{D}_t$ picking out even samples of $\mathbf{P}\mathbf{c}_t$. Most perfusion estimates are based upon filtered subtraction methods that attenuate the un-modulated terms $s_m M_0 \mathbf{b} + s_q \mathbf{q} \circ \mathbf{b}$ in the GLM (corresponding to BOLD weighted static tissue and perfusion terms) while preserving the modulated term $\alpha \exp(-TI/T_{1B})\mathbf{M}(\mathbf{q} \circ \mathbf{b})$ (corresponding to a BOLD weighted perfusion term) [3]. This process can be expressed as a modulation operation followed by a low pass filtering operation [3]

$$\hat{\mathbf{q}} = \mathbf{GMy} \approx \mathbf{G}(\mathbf{q} \circ \mathbf{b}) + \mathbf{GU}_c\mathbf{D}_c\mathbf{P}\mathbf{c}_c - \mathbf{GU}_t\mathbf{D}_t\mathbf{P}\mathbf{c}_t + \mathbf{n}$$

where $\hat{\mathbf{q}}$ is a BOLD-weighted and filtered version of the true perfusion signal **q**, **G** is a low pass filtering matrix, **n** is the additive noise after modulation and filtering, and for convenience we have dropped the $\alpha \exp(-TI/T_{1B})$ constant term. To form a general linear model, we assume that the BOLD-weighted perfusion term $\mathbf{q} \circ \mathbf{b}$ can be expressed as the sum of a constant term $\mathbf{q}_0$ and a dynamic term **Xh** where **X** is a *Nxk* design matrix and **h** is a *kx1* vector of hemodynamic parameters. The constant term $\mathbf{q}_0$ plus other low frequency confounds are modeled as **Sd**, where **S** is a *Nxl* matrix comprised of *l* nuisance model functions and **d** is a *lx1* vector of nuisance parameters. Integrating these components yields the general linear model (GLM)

$$\hat{\mathbf{q}} = \mathbf{GXh} + \mathbf{Sd} + \mathbf{GU}_c\mathbf{D}_c\mathbf{P}\mathbf{c}_c - \mathbf{GU}_t\mathbf{D}_t\mathbf{P}\mathbf{c}_t + \mathbf{n}$$

Methods

Experimental Protocol: A visual stimulation study was performed with the use of a black and white radial checkerboard flashing at 8 Hz presented in a block design paradigm consisting of 4 cycles of 20s stimulation with 40s rest. Six subjects (age 24-35) underwent 4 repeats of the block design. A hippocampal study was also performed in seven subjects (age 21-31) and consisted of subjects viewing alternating 25 second blocks of familiar and novel landscape scenes. This paradigm was repeated 3 times for each subject.

Image acquisition: Scanning was performed on a 3T GE Signa whole body system, with a body transmit coil and an 8 channel receive only head coil. A PICORE QUIPSS II [5] sequence was used with a dual gradient echo spiral readout. Imaging parameters for the visual stimulus were: TR=2s, TI1=600ms, TI2=1500ms, Flip angle = 90°, FOV = 24x24 cm2, matrix size 64x64, TE1=9.1ms, TE2=30ms, with four 7mm slices positioned through the primary visual cortex at an oblique angle parallel to the calcarine sulcus. The tagging band was 100 mm thick, positioned 10mm from the proximal edge of the first slice. Hippocampal parameters were TR=3s, TI1=700ms, TI2=1400ms, TE1=2.8ms, TE2=24ms, and a 200 mm tag. Five 6 mm slices were positioned though the hippocampus. Cardiac pulse and respiratory effort data were recorded continuously.

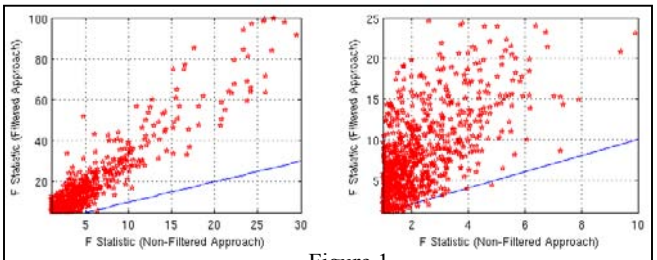

Figure 1.

	Mean F statistic *Unfiltered Approach*	Mean F statistic *Filtered Approach*	Significantly different
Visual cortex data	6.8	23.17	p<1e-60
Hippocampal Data	1.08	4.689	p<1e-45

Statistical comparison: In order to compare the relative performance of the unfiltered and filtered methods, F-statistics were computed using a reference function (smoothed block design) as the regressor of interest. For each subject, we defined a functional region of interest (ROI) consisting of the union of all voxels that passed the threshold (F=1 for hippocampal data and F=5 for visual cortex data) using either the unfiltered or the filtered approach.

Results

Figure 1 shows F-statistics obtained with the proposed filtered approach (y-axis) vs. F-statistics obtained with the previous unfiltered approach (x-axis) for one subject from each of the visual cortex (left) and hippocampal (right) protocols. The table shows mean F-statistics for each condition. The F-statistics for the filtered approach were significantly (p<1e-45) greater than those for the unfiltered approach in both the hippocampal and visual cortex data. Similar results were seen across all subjects.

Discussion

Using the filtered approach resulted in an approximately four fold increase in the F-statistic. This reflects the fact that the previous unfiltered approach was based on the difference (resulting in a factor of 2 increase in variance) of two estimates (tag and control), each of which had twice the variance (since they only used half of the available data) of an estimate based on all the images. Thus, the filtered approach should be used for the reduction of physiological noise in ASL data.

References

[1] Glover, G.H. et al., MRM 44:137-143 [2] Restom, K. et al., Proc ISMRM 2003, 2525 [3] Liu et al., NIMG 24: 207-215, 2005.