Regional heterogeneity in vascular response to respiratory challenges as measured with BOLD fMRI

M. G. Bright[1,2], S. G. Horovitz[1], P. Jezzard[2], and J. H. Duyn[1]

[1]Advanced MRI section, Laboratory for Functional and Molecular Imaging, NINDS, National Institutes of Health, Bethesda, MD, United States, [2]Department of Clinical Neurology, Oxford Centre for Functional MRI of the Brain, University of Oxford, Oxford, United Kingdom

Introduction

Measuring the cerebral blood flow response to changes in arterial gas tensions provides insight into the complex nature of healthy vasculature and could possibly offer a diagnostic tool for examining pathologies linked to stroke or other vascular disorders. Hyper- and hypocapnia in conjunction with noninvasive MRI techniques are frequently employed to assess this cerebrovascular reactivity in normal and patient populations. Arterial spin labeling (ASL) imaging is a direct method for quantifying flow changes, but suffers from low SNR and limited brain coverage. Blood oxygenation-level dependent (BOLD) contrast MRI has higher SNR and better temporal resolution and coverage of the brain. However, most BOLD reactivity studies use blocks of carbogen inspiration or extended hyperventilation (Krainik et al.), which are not ideal candidates for use in the clinical setting, and while previous research using breath holding has successfully identified general vascular abnormalities in disease states by analyzing percent signal change (Shiino et al.), the timing of the response to such respiration challenges may be equally valuable in diagnosing threatened tissue (van Osch et al.). The goal of this study is to characterize the transient BOLD response to simple respiration tasks to obtain both magnitude and timing information at the voxel level. The work presented here examines short breath holds and deep breaths as potential candidates for a clinical reactivity assessment test and introduces a flexible fitting procedure to quantify the resulting signal changes.

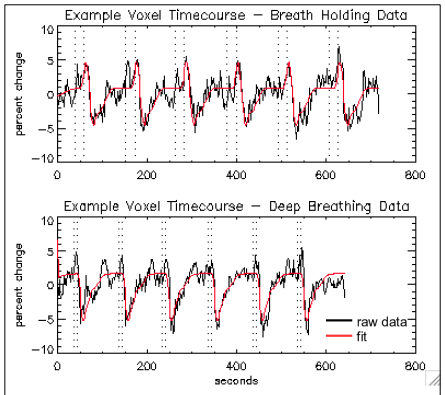

Figure 1: Example grey-matter voxel timecourses from breath holding (top) and deep breathing (bottom) scans and the fitted timecourse found using FLOBS. Dotted lines represent the duration of the respiration challenge. The signal decrease immediately following the hypercapnia-induced signal increase in the breath holding data is likely due to the deep breaths taken by the subject upon resuming of normal breathing.

Methods

13 healthy volunteers were scanned using a 3 Tesla GE scanner equipped with a 16-channel receive coil (Nova Medical). Whole-brain BOLD fMRI data were collected with a standard EPI sequence (TE: 40 ms, TR: 2 s, 24 slices, 2.29 x 2.29 x 5 mm). Cardiac data were acquired using a pulse oximeter and respiration was assessed using a respiratory belt and end-tidal CO_2 monitor (Biopac). Slice timing and motion corrections were performed using SPM, and distortion and physiological noise corrections were done using in-house procedures (IDL). To separately study mild hypercapnia and hypocapnia, we used two distinct respiratory challenges: a) 20 second breath hold without preparation (series of six, 90 seconds recovery in between), and b) 2 cycles of deep breaths (series of six, 90 seconds recovery). All breathing during the challenges was cued, and subjects were trained and given time to practice before entering the scanner. During the recovery and breath hold periods subjects completed a "1-back" working memory task in order to create a more standardized baseline condition across the study.

To analyze the BOLD signal response to the breathing challenges, we adapted FLOBS (FMRIB's Linear Optimal Basis Sets, part of FSL, (Woolrich et al.)) to allow a flexible model for independently fitting each voxel timecourse. Using four partial cosine functions in series with a variable initial delay, limiting timing and amplitude parameters to ranges provided by the user, FLOBS is primarily intended to offer a flexible HRF made from an optimal set of basis functions that makes the General Linear Model more sensitive to changes in the hemodynamic response. Here, the same functional form was adapted using ranges estimated from our data before being convolved with our respiration paradigm, and we obtained the fitted response function for every voxel in the brain in both our breath holding and deep breathing data. The fitted functions were then analyzed to measure amplitudinal changes in signal, relative timing, and other characteristics reflecting the shape and strength of the BOLD response.

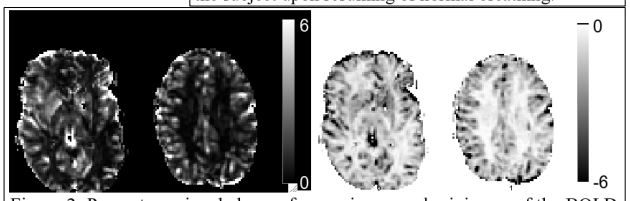

Figure 2: Percentage signal change for maximum and minimum of the BOLD response to breath holding (left) and deep breaths (right), respectively.

Results

The basis sets we produced with FLOBS were successful in fitting voxels throughout grey matter, allowing for reasonable variation in the timing and magnitude of the BOLD response (Fig. 1). Two cycles of comfortable deep breathing (cued as "breathe in, breathe out, breathe in, breathe out, breathe normally) resulted in a short-lived decrease of ~0.6-1.0% end-tidal fraction of CO_2 and a BOLD signal change of approximately the same magnitude as the breath hold: data for a single subject are shown in Figure 2, and in a preliminary analysis of five subjects, average signal changes in grey matter for deep breathing and breath holding were -2.9 and +3.0 percent, respectively. While this phenomenon has been seen in previous studies, we believe it has yet to be explored for it's clinical and diagnostic potential. By measuring the timing of the minimum of the fitted BOLD signal decrease, we obtain whole-brain maps that indicate reasonable regional differences in the healthy response delays (Fig. 3). Further research will be done to explore the sensitivity of this fitting technique in identifying response abnormalities associated with pathologies in transient ischemic attack patient populations. It should be noted that, as predicted, voxels that did not show significant effects related to the six respiratory challenges (e.g. white matter) were not well fit by this technique, and cannot be accurately included in this analysis process.

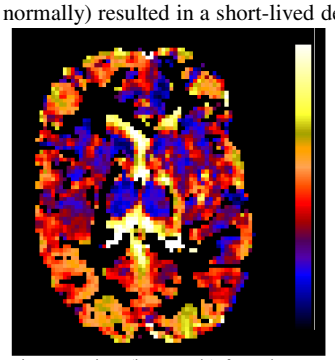

Figure 3: Time (in seconds) from the start of deep breaths to the minimum of the BOLD signal decrease, obtained using the FLOBS fitting results. In other subjects, maps of relative timing of the BOLD signal dip after deep breaths show similar regional heterogeneity, possibly indicating early response in the thalamus, caudate, and putamen (as suggested here).

Conclusions

The simple task of deep breathing for two cycles results in a surprisingly strong BOLD signal response, on par with traditional breath holding and gas inspiration challenges. While this process reflects a separate, vasoconstrictive aspect of vascular reactivity as opposed to the traditional vasodilatory response to hypercapnia, it is exciting to observe such a clinically-suitable task elicit such robust responses. Also, by fitting the complex signal changes caused by both short-lived breathing tasks using FLOBS, we are able to access relevant parameters for describing healthy and potentially pathologic variations in reactivity throughout the whole brain.

References

Krainik A et al. *Proc. ISMRM*. **15** (2007)

Shiino A et al. *JCBFM* **23**, No.1 (2003)

van Osch et al. *NeuroImage* **17**, 469-478 (2002)

Woolrich M et al. *Neuroimage* **21**(4):1748-1761 (2004)