Characterizing the BOLD response to transient respiratory challenges at 7 Tesla

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Introduction. Cerebrovascular reactivity (CVR) to changes in arterial gas tensions can offer insight into the compliance and health of blood vessels and assist in clinical diagnosis and prognosis of patients with hemodynamic pathologies [4]. We have recently introduced a new, clinically appropriate respiratory challenge of Cued Deep Breathing (CDB) that causes transient hypocapnia, and explored the regional heterogeneity in the BOLD response amplitude and dynamics in healthy volunteers at 3 Tesla [2]. The BOLD response to the challenge revealed consistent spatial patterns of early and delayed response timings across subjects, but individual subject maps of these parameters were often confounded by noise. A more robust technique for analyzing the physiologically relevant characteristics of the CDB BOLD response would enable better implementation of the CDB challenge in individual patient studies. In an fMRI study by Birn et al. [1], respiration was rigorously supervised and the shape of whole-brain BOLD response to a single deep breath was extracted to create a Respiration Response Function (RRF). The RRF is described as a difference of two gamma-variate functions: $RRF(t)=a_1t^{b1}\exp(-c_1/t) - a_2t^{b2}\exp(-c_2/t)$ and variables were empirically determined in healthy subjects. This function exhibits a biphasic response, which is sometimes present in the CDB data, and correlation with voxel timecourses indicates a range of optimal latencies of ± 8 s across the brain, similar to our own findings in CDB time-to-peak (TTP) maps [1]. In this study, we modify the empirically derived RRF proposed by Birn *et al*. to fit the CDB BOLD response at 7 Tesla. The higher magnetic field strength increases BOLD CVR [3] and the multiple deep breaths of the CDB challenge are likely to cause greater $P_{ET}CO_2$ changes than the single breaths in the original RRF studies. These factors may improve our ability to discern voxel-wise dynamic characteristics such as onset timing and response width, which may be more physiologically relevant parameters than TTP. By understanding the heterogeneity and relationships of these parameters in healthy subjects, we enable better interpretation of abnormal responses in individual patient data.

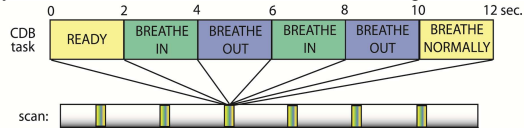


Figure 1.: Schematic of Cued Deep Breathing challenge cues

Methods. ***Data Acquisition:*** Nine subjects were scanned using a 7 Tesla GE whole-body scanner (Milwaukee, WI, USA) equipped with a 32-channel receive head coil. Subjects were cued to execute six CDB challenges interleaved with 75 seconds of normal breathing using the text-based stimuli shown in Fig 1. Data were acquired using a BOLD-weighted gradient-echo EPI sequence (TR/TE=2000/30 ms, FOV=240 mm, slice thickness/gap=3 mm/1 mm, 330 repetitions) for a total scan duration of 11 minutes and an in-plane resolution of 1.88 x 1.88 mm^2. A 4 minute reference EPI scan was collected prior to the functional scan during concurrent respiratory monitoring via chest bellows, and was used to implement real-time shimming to reduce respiration-driven scanning artifacts during the functional scan [5].
Data Analysis: Data were preprocessed (motion and slice timing correction, brain extraction, detrending, *FSL*). The starting times of each challenge were identified using the bellows trace, and the nearest fMRI volume was determined for each trial. A 40-volume (80 s) window of the BOLD data was extracted for each trial. The difference between the bellows-defined trial starting point and the nearest fMRI volume was calculated and used as a trial-specific shift in the time vector. Because the challenge used in our study is not identical to the single deep breath used to derive the original RRF, a lag term was incorporated to enable more flexibility. The baseline BOLD signal level was also fitted for, rather than extracted directly from a portion of the data. The modified RRF, defined as:

$$RRF(t_0+t_{lag})=a_1t^{b1}\exp(-c_1/t) - a_2t^{b2}\exp(-c_2/t)+\text{baseline}$$

was used to fit the combined CDB BOLD data. The maximum (negative) % signal change, time-to-peak, onset timing (defined as when the signal decreases from baseline to 5% of the CDB response) and the full-width-half-minimum (FWHM) of the CDB signal dip were extracted from the fit results. Because the modified RRF allows for biphasic responses, the amplitude of the initial signal increase preceding the expected CDB BOLD decrease was also extracted.

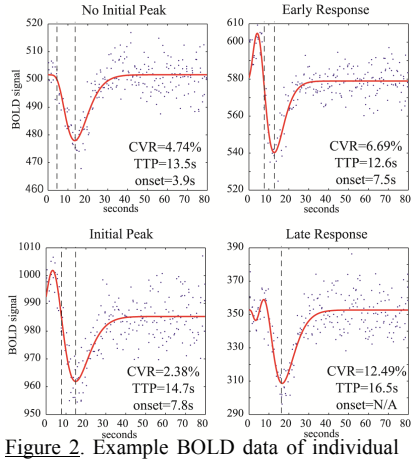


Figure 2. Example BOLD data of individual voxels and resulting RRF fits.

Results. An example of original BOLD data and resulting RRF fits for individual voxels is given in Fig. 2. The small BOLD signal increase preceding the dip associated with the hypocapnic CDB challenge is present in some, but not all, responsive voxels. Examples of all parameters extracted using the RRF fitting are shown in a single slice of one subject in Fig 4. The fitted CDB RRFs exhibit deviations from the original RRF described by Birn *et al*. [1] in response to a single deep breath: Fig. 3 illustrates the distribution of our fitted parameters with the original empirically derived values for comparison.

Discussion. Using high-field BOLD fMRI data, a novel hypocapnia respiratory challenge, and a more sophisticated fitting procedure, we successfully mapped voxelwise reactivity and TTP in the whole brain. We also extracted onset timing and response width, which may better reflect physiological changes in the presence of disease. These parameter maps exhibit comparable regional heterogeneity as the TTP map, suggesting the more robust TTP measurement can be used as a faithful surrogate marker for the more subtle dynamic parameters. Further work involving distortion correction and increased number of trials is needed to determine if there is a consistent spatial pattern in the magnitude of the initial BOLD signal increase peak, which exhibited large inter- and intra-subject variability. The double gamma variate RRF function was successful at fitting the full range of voxel responses present in our data. However the number of free parameters used in the fitting process allows for redundancy in the function shape, and suggests that the absolute parameter values should not be directly compared for robust interpretation of the response dynamics. For example, much of the discrepancy between the original RRF and the fitted CDB RRFs can be approximated by adjusting the a_2 value, but all parameters, not just a_2, are altered in CDB-optimized fitting at 7 T (Fig 3).

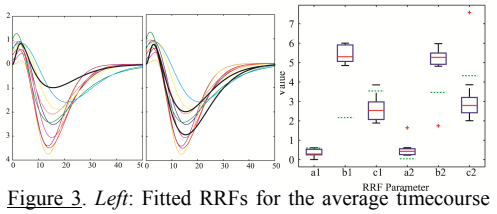
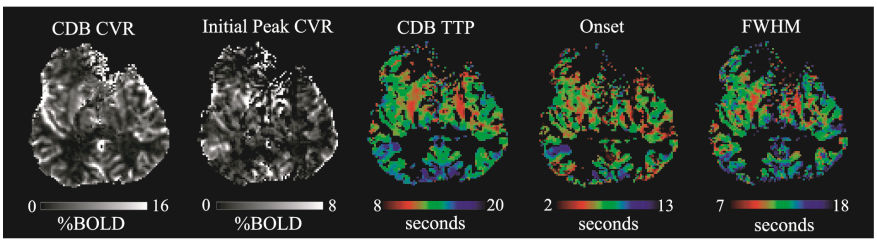


Figure 3. *Left*: Fitted RRFs for the average timecourse of 9 subjects (color) compared with the RRF in response to a single deep breath [1] (black), plotted as %BOLD versus scan volume. *Center*: Manual alteration of the a_2 parameter of the original RRF [1] ($2a_2$ and $3a_2$, black lines) suggests this parameter explains much of the difference in response dynamics. *Right*: Boxplots of fitted parameter values for nine subjects compared with the original parameter values (green).
Figure 4. *Below*: CVR (%BOLD) and temporal parameter maps for one subject.

Conclusions. This study further establishes the consistent regional patterns in CVR dynamics observed previously at 3 Tesla, and supports the use of CDB challenges in robust mapping of whole brain, voxelwise cerebrovascular reactivity. The TTP metric offers a robust alternative to onset time and FWHM parameters in individual subject maps.



Bibliography.
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