Dynamics of CBF and BOLD responses to a Cued Deep Breathing paradigm

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Introduction: Respiratory challenges have been used for inducing a vascular response in the brain, causing variations in cerebral blood flow (CBF) and cerebral blood volume, while the oxygen consumption remains constant, which also produces Blood Oxygen Level Dependent (BOLD) signal changes. Modeling the CBF and BOLD responses to respiratory challenges can be achieved by convolving an impulsive response function (IRF) with a waveform describing the respiratory paradigm. Although the shape of this IRF has been determined analytically [1], it is usually approximately modeled by a Gamma function. However, the parameters characterizing such Gamma IRF have not been thoroughly investigated. In this study, we propose to characterize the dynamics of the cerebrovascular response to a cued deep breathing (CDB) challenge [2] measured with both Arterial Spin Labeling (ASL) CBF and BOLD fMRI signals, by searching the Gamma IRF parameter space using a General Lineal Model (GLM) approach.

Methods: A group of 5 healthy volunteers were scanned on a 3T Siemens Verio system using a 12-channel head RF coil. Whole brain BOLD fMRI data were collected with GE-EPI (TR/TE=2500/50 ms, 3.5x3.5x7.0 mm^3). Pulsed ASL data were collected using a Q2TIPS-PICORE sequence [3] with GE-EPI (TR/TE=2500/25 ms, TI1/TI1s/TI2=750/900/1700 ms, 3.5x3.5x7.0 mm^3), from 9 contiguous axial slices positioned parallel to the AC-PC line. A FOCI 180° inversion pulse was applied to a 10cm thick labeling region, positioned 18.8mm below the proximal imaging slice. An MPRAGE structural image (TR/TE=2250/2.26 ms, 1x1x1 mm^3) was also obtained.

A CDB fMRI paradigm was designed as illustrated in Figure 1: 25s of initial rest; 40s of CDB alternated with 60s of self-paced breathing (ASL/BOLD=3/2 cycles). The deep breathing cues were presented visually by alternating inspiration (2s) and expiration (3s) instructions. Subjects' compliance to the task was monitored using a respiratory belt placed around the base of the chest. The acquisition of BOLD and ASL data was counterbalanced across subjects.

A GLM method, performed using FEAT from FSL, was used to find the optimal Gamma IRF parameters, both on a whole-brain and on a voxel-by-voxel basis. The Gamma IRF parameters were systematically varied: time to maximum (or *lag*, varied from 5 to 60s in steps of 5s) and width (or *sigma*, varied from 2.5 to 30s in steps of 2.5s), based on a previous study [4]. For the BOLD signal, the explanatory variable was described by CDB periods convolved with each Gamma IRF. For the CBF-based signal, an additional explanatory variable was defined to describe the alternation between tag and control volumes and the interaction between this and the previously described explanatory variable was considered. The activation maps for each *lag* and *sigma* were obtained by cluster threshold with voxel $Z>2$ and cluster $p<0.05$. For the whole-brain analysis, the *lag* and *sigma* pair which yielded the maximum number of active voxels was selected, for each subject and sequence. For the voxel-by-voxel analysis, the *lag* and *sigma* pair producing the highest Z statistic value was selected for each voxel, resulting in optimal *lag* and *sigma* maps, for each subject and sequence. The individual maps were registered to the MNI standard brain using FLIRT from FSL and then averaged over the five subjects.

Results: The number of activated voxels obtained for each *lag* and *sigma* is shown in Figure 2, for one representative subject. Different patterns are observed for BOLD and CBF data, with CBF responses exhibiting a trend towards lower optimal lags and longer optimal widths than BOLD responses. For both techniques, a wide region of optimal *lag* and *sigma* pairs can be identified, suggesting that different combinations of the two parameters could describe the Gamma IRF. This is probably a result of the fact that a block design paradigm was employed. In fact, the ideal paradigm design for IRF estimation would consist of single deep breaths [1]. In our study, shorter CDB durations of 10 and 20s were also investigated and, in fact, the observed uncertainty on the optimal IRF parameters obtained for each *lag* and *sigma* was reduced (results not shown). However, although the regional *lag* and *sigma* maps obtained with lower CDB durations were not significantly different from the 40s duration paradigm, the lower SNR of the ASL data obtained in these cases was not sufficient to successfully detect the expected activation areas. Across the group, the IRF parameter values that produced the highest numbers of activated voxels were *lag*=26.0±5.5s/28.0±24.9s and *sigma*=16.5±5.7s/22.5±9.3s, for BOLD and ASL, respectively. An example of the activation statistic Z maps obtained for one subject with the voxe-by-voxel optimal parameters, for both BOLD and CBF data, is shown in Figure 3. The group average optimal *lag* and *sigma* maps obtained by the voxel-by-voxel analysis are shown in Figure 4. Some degree of heterogeneity was observed, with longer lags in the posterior brain region.

Discussion: The characterization of a Gamma impulsive response function for BOLD and CBF measurements induced by a CDB challenge allows a more sensitive detection of the activated regions and a more accurate measurement of the associated cerebrovascular reactivity (CVR). Due to the observed spatial heterogeneity of the response timing parameters, consistent with previous findings [1,2], a voxel-by-voxel optimization of the IRF is more appropriate. Besides characterization of the activation region in terms of Z statistic and percent signal change, a voxel-by-voxel analysis produces optimal *lag* and *sigma* maps, which may be modified in pathology. Comparison between the BOLD and CBF Gamma IRF optimal parameters suggests different dynamics, with a trend for CBF to exhibit a faster response to a CDB challenge.

References: [1] Birn, NI 2008; [2] Bright NI 2009; [3] Luh MRM 1999; [4] Grouiller HBM 2010.

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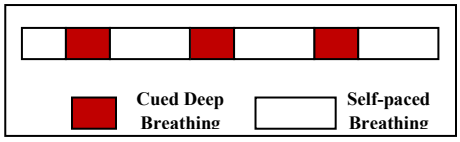

Figure 1: CDB paradigm scheme.

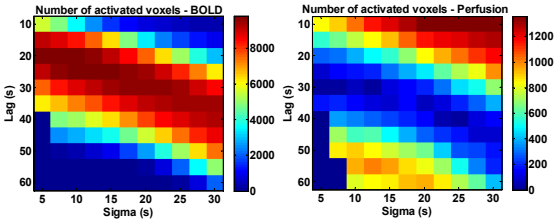

Figure 2: Number of activated voxels for each *lag* and *sigma*, for BOLD and CBF, in one subject.

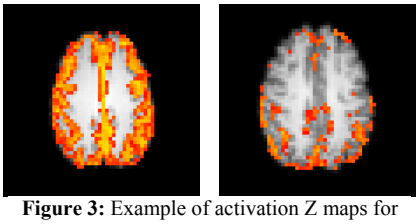

Figure 3: Example of activation Z maps for BOLD (2<Z<12) and CBF (2<Z<7).

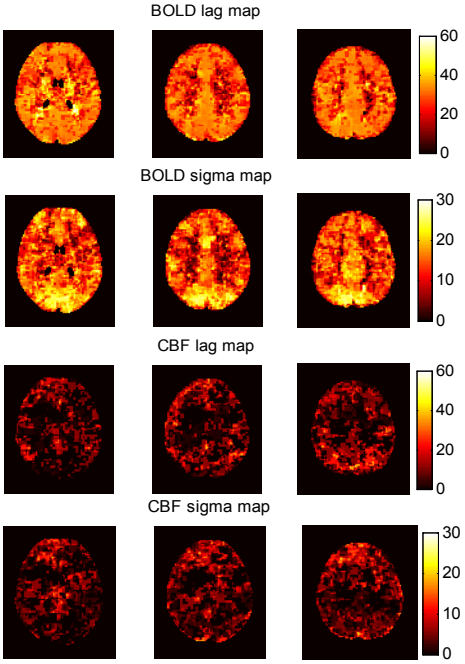

Figure 4: Optimal *lag* (s) and *sigma* (s) maps for BOLD (top) and CBF (bottom) responses averaged across subjects in MNI space.