Reproducibility of BOLD signal change induced by breath holding

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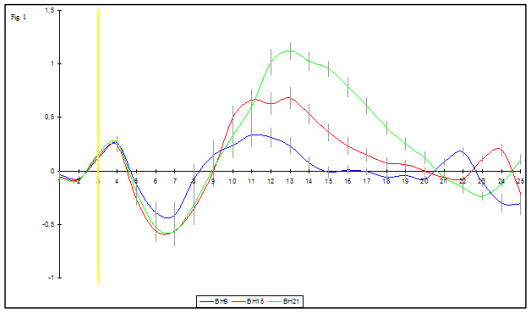
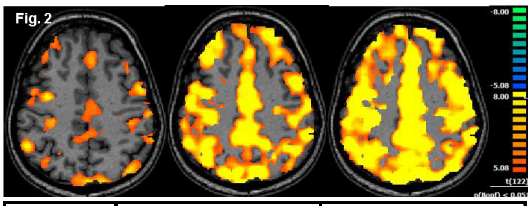
Introduction

Subject-specific neurovascular reactivity can be used to correct BOLD (Blood oxygen level-dependent) fMRI activation maps reducing the variance due to differences in MR equipment [1] and to differences in vascular response among subjects [2]. Thus it would be desirable to have a reliable and simple method to investigate vascular reactivity. Neurovascular reactivity can be efficiently investigated inducing a mild hypercapnia either by CO2 inhalation or by breath holding (BH). The latter method is simpler to perform and less invasive and could be applied in almost any clinical or experimental setting. However, no studies in the literature explored the reproducibility of BOLD BH-induced response. The aim of the present work was to investigate the variability and reproducibility of BOLD signal changes, within and across subjects, in response to different BH durations.

Methods

Eleven subjects (6 females, 5 males) were scanned with a Siemens Allegra 3.0T MRI Unit. T2* weighted gradient-echo EPI (TR=3000 ms, TE=30 ms, flip angle=90°, 64x64 in-plane resolution, FOV= 192x192, number of slices = 36 interleaved transversal, slice thickness = 3 mm, gap = 10% , bandwidth 1986 kHz, 124 whole brain volumes were acquired) and high resolution T1-weighted 3D MPRAGE sequences were acquired (TR=2300 ms, TE=2.93 ms, voxel size=1x1x1 mm).
Subjects were asked to hold their breath for 9, 15 or 21 seconds (BH9, BH15 and BH21) in three different runs. During each run subjects performed 5 breath hold periods of the same duration alternating them with 42 seconds of self-paced breathing. Performance was monitored using an elastic belt placed around the abdomen. Subjects repeated the same protocol after 15-20 days. The order of the three runs was balanced among subjects. Data were elaborated using BrainVoyager® (BVQX 1.8.6 for Windows XP. Brain Innovations, Maastricht, The Netherlands). Pre-processing fMRI data consisted in slices scan time correction, 3D motion correction (intra-section alignment), spatial smoothing (FWHM=5) and temporal filtering (high-pass filter 0.0063 Hz and linear trend removal). fMRI data were co-registered with the subject's 3-D anatomical dataset. High resolution anatomical data were segmented to extract cortical grey matter.
All analyses were performed taking into account only cortical grey matter. Signal changes were averaged on the 5 breath hold periods for each run (Fig 1). Percent Signal Change (PSC), Time To Peak (TTP) and Integral of Subtended Area (Area) were calculated for each of the 3 resulting curves. Furthermore, a voxel by voxel model-drive approach (General Linear Model) was applied in order to calculate the number of activated voxels (activation volume). Regressors for each run were modelled as a boxcar function convolved with a two-gamma function (HRF); the delay of the HRF was computed specifically for each subject using a Cross-Correlation analysis. Statistical analyses of signal parameters were performed using ANOVA for repeated measures.
In order to evaluate BOLD signal reproducibility, both Inter-Subjects Coefficient of Variation (CVinter; [3]) and Intra-Subjects Coefficient of Variation (CVintra; [4]) were computed.





Tab.1

	CVintra			CVinter		
	BH9	BH15	BH21	BH9	BH15	BH21
Area	38%	29%	11%	63%	45%	29%
PSC	28%	22%	6%	55%	34%	21%
TTP	6%	6%	5%	36%	14%	10%
Act. Vol.	46%	27%	15%	87%	63%	26%

Fig.1 Average signal of BH9 (blue), BH15 (red) and BH21 (green) for all subjects. The yellow line shows the breath hold starting point. **Fig.2** Example of differences in a subject's activation volume. From left to right: breath holding duration 9, 15 and 21 sec. **Tab.1** Coefficient of Variation intra-subjects (CVintra) and Coefficient of Variation inter-subjects (CVinter). Area= Integral of Subtended Area, PSC= Percent Signal Change, TTP= Time To Peak and Act.Vol.=Activation

Results

All subjects performed all tasks without discomfort but reported that holding breath for 21 sec was more difficult than all other BH durations. Furthermore, the most chest movements were noticed during this condition.
The curves of the fMRI signal change show a triphasic structure for all BH durations (Fig 1). After an initial short positive phase, the signal becomes negative and starts to increase after 10 sec becoming again positive between 18 and 21 sec from the start of the breath hold. This portion of the curve is not significantly different among the three BH durations. On the contrary, the PSC, TTP and Area of the third positive portion of the curve were all significantly different (average $p < 0.001$) among the three BH durations.
The activation volume (Fig. 2, $p<0.05$ corrected) was significantly different between each condition against each other ($p < 0.001$).
The reproducibility of BOLD BH-induced response (Tab. 1) is dependent on the duration of breath hold. Intra and Inter-Subject Coefficients of Variation (CV) decrease as breath hold duration increases. Data show more variability across subject pool (CVinter) compared to variability between sessions (CVintra). BOLD BH-induced signal parameters show different CV: Activation Volume and Area show higher CVintra-subjects and CVinter-subjects. TTP and PSC of signal show lower variability between sessions and across subject pool.

Conclusions

The first two portions of the BOLD signal curves are likely to be related mostly to the subject's preparation for the breath hold that induces physiological variations (such as chest expansion, heart rate decrease, etc) that reflects upon the cerebral blood flow. Their effect on the BOLD signal is significant but invariant in terms of timing, phase and amplitude across BH durations so that it can be easily discarded during data analysis. The main effect of BH on BOLD signal is reflected on the third portion of the curves and happens at least 18 sec from the start of the BH, independently from the time at which the subjects restart the self-paced breathing pattern. The reproducibility of this effect is directly dependent on the duration of the BH being higher for longer BH durations, possibly because subject's brain vascular reactivity is pushed toward its maximum.

References

1. Cohen ER *et al*, *NeuroImage* 23, 2004.
2. Thomason *et al*, *Human Brain Mapping* 28, 2007.
3. Tjandra T. *et al*, *NeuroImage* 27, 2005.
4. Leontiev O. and Buxton B.R., *NeuroImage* 35, 2007.

Grant Support
This work was partially financed by *Merrill Lynch International*