# Saturation of visually evoked BOLD response during carbogen inhalation

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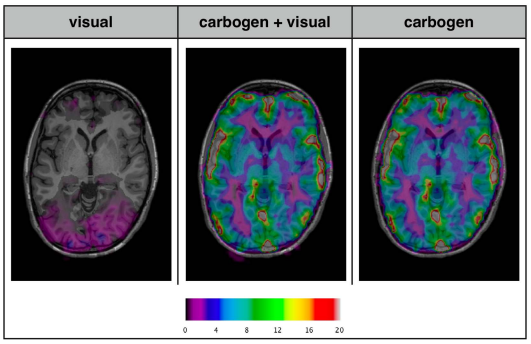
**Introduction:** The BOLD (Blood oxygenation level dependent) signal is inherently ambiguous, reflecting a combination of metabolic and vascular responses. Changes in oxidative metabolism can be estimated from the BOLD signal using calibration methods described previously [1,2]. These calibration procedures typically involve estimating a parameter M, which is equivalent to the maximum possible BOLD signal change that would occur upon complete removal of all deoxygenated hemoglobin from the brain. In previous reports, M has been extrapolated from smaller signal changes induced by hypercapnia [1,3] or hyperoxia [2]. A more robust approach would be to increase flow and oxygen saturation sufficiently to drive the venous $O_2$ saturation close to 100%, allowing direct measurement of the BOLD plateau. Breathing carbogen (5 or 10% $CO_2$ in balance $O_2$) leads to increased oxygen saturation from the large $O_2$ concentration, accompanied by increased blood flow from the presence of $CO_2$ [4]. Carbogen was used here in combination with intense visual stimulation to test whether an asymptote in the total BOLD signal could be reached.
**Methods:** Acquisitions were conducted in three subjects on a 3T MRI system. Sessions included an anatomical, 1mm$^3$ MPRage acquisition (TR/TE/alpha = 2300ms/3ms/90°, 256x240 matrix) and nine BOLD functional runs (TR/TE/alpha = 2000ms/30ms/90° with 4x4x4mm voxels, 64x64 matrix and 33 slices). During BOLD acquisitions, all subjects underwent a titration with 10% carbogen (10% $CO_2$, 90% $O_2$). A second session was done in two subjects with 5% carbogen (5% $CO_2$, 95% $O_2$) to see if similar BOLD changes could be reached with a lower $CO_2$ concentration, but similar $O_2$ levels. Four carbogen fractions (25%, 50%, 75%, 100%) with balance air were tested, in a single 3-minute block per run. One run per carbogen concentration had in addition a 1-minute visual stimulus block (8Hz black and white, flashing checkerboard), starting 30s after the beginning of the carbogen block. Gases were adjusted manually using flow-meters to keep a total flow rate of 16L/min at all times. The order of the BOLD runs for each carbogen concentration was randomized between subjects. Data were motion corrected and spatially smoothed with a 6 mm 3D Gaussian kernel. A general linear model (GLM) with canonical hemodynamic response function (HRF) as a single gamma function and a linear drift term was applied, to obtain effect sizes for each stimulus (visual, carbogen and carbogen+visual).
The first 60 s after breathing-gas transitions were excluded from the analyses to sample the peak gas response (which occurred after 60 s). Regions of interest (ROI's) were derived from thresholded ($p<0.05$ corrected) visual activation maps. Percent changes were then calculated by dividing effect sizes over the visual ROI by the constant term from the GLM over that region.
**Results:** Inhalation of 10% carbogen caused large BOLD signal increases in cortical and sub-cortical grey matter, with the incremental contribution from addition of visual stimulation becoming successively smaller at higher concentrations (Fig. 1). Fractional titration of carbogen led to a progressive increase in BOLD signal (Fig. 2A). Signal changes associated with the combined carbogen and visual stimuli converged towards the maximal signal change observed with 10% carbogen alone, both at the average and individual subject level (Fig. 2). The signal changes evoked by the combination of 5% carbogen and visual stimulation also converge towards the same maximum, although 5% carbogen alone does not reach this level (Fig. 2B).
**Discussion:** The results show a convergence of BOLD percent signal changes at around 9% in visual cortex for 10% carbogen alone, as well as for 10% and 5% carbogen breathing combined with intense visual stimulation (Fig. 2). The diminishing incremental response from visual stimulation at high carbogen concentrations suggests that these three manipulations approach BOLD levels close to the saturation plateau (i.e. close to M). The high blood oxygenation and flow values achieved with 5% carbogen breathing have been shown before to lead to an almost complete loss of susceptibility contrast in MR venography images [5]. The higher $CO_2$ content of the carbogen used here and the combination with visual stimulation yield even larger BOLD changes (Fig. 2B). The results shown here put a lower bound of 9.2% on M in visual cortex under the conditions of our experiment (TE=30ms, 3 Tesla). This is in the middle range of literature values reported for similar populations (Table 1).
**References:** [1] Davis, TL et al., *PNAS* 95, 1834-9 (1998); [2] Chiarelli, PA et al., *Neuroimage* 37(3), 808-20 (2007); [3] Hoge, RD et al., *PNAS* 96, 9403-8 (1999); [4] Ashkanian, M et al., *Neuroscience* 156(4), 932-8 (2008); [5] Sedlacik, J et al., *Neuroimage* 43, 36-43 (2008)

**Figure 1. Percent BOLD change maps for each stimulus**



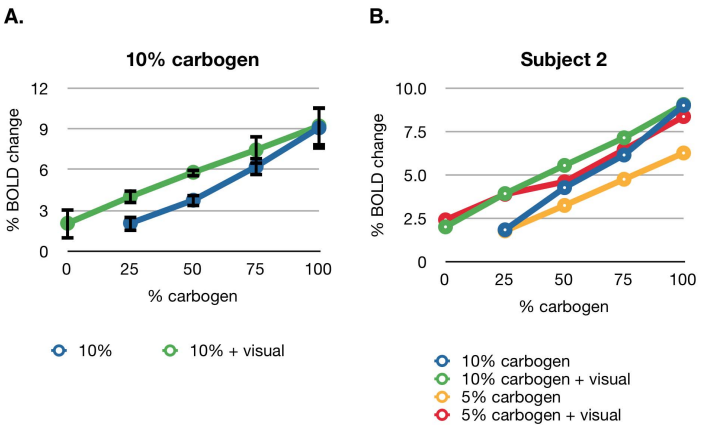

Example percent BOLD effect maps from one subject for each stimulus type. The carbogen and carbogen + visual maps show the results for the highest fractional concentration of 10% carbogen. The visual map shows the response to the visual stimulus alone.

**Table 1. Literature M values for visual cortex at 3T**

| | Calibration technique | M |
|---|---|---|
| Chiarelli 2007 | HO | 7.0 |
| Leontiev 2007 | HC (5%) | 11.1 |
| Ances 2008 | HC (5%) | 6.5 |
| | | 7.3 |
| Lin 2008 | HC (5%) | 10.5 |
| Perthen 2008 | HC (5%) | 11.6 |
| | | 12.1 |
| Bulte 2009 | HC (4%) | 5.3 |
| Chen 2009 | HC (5%) | 6.7 |

Literature M values from studies in visual cortex at 3T. Values were converted to reflect a TE of 30ms. HC=hypercapnia, HO=hyperoxia. The M value of 9.2 found here is in the middle range of literature values.

**Fig. 2 Signal changes in response to carbogen and visual stimulation**




**A**. Average percent BOLD signal change over subjects associated with 10% carbogen breathing with and without visual stimulation over visual ROI. Percent BOLD signal converges towards a point around 9%, indicating possible saturation of the signal. **B**. Percent BOLD signal changes for an example subject, for both 5% and 10% carbogen, with and without visual stimulus for an example subject. The trend in the average is also visible here and 5% + visual also converge to the same value.