# Normalisation of BOLD FMRI data between different baseline conditions using hyperoxia

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**Introduction**

BOLD FMRI is highly sensitive to alterations in baseline physiology. Many common substances are known to change blood flow either directly or indirectly; these include caffeine, antihistamines, opioids and nicotine. The effects of these blood flow changes can be a significant confound to the efficacy of BOLD FMRI for clinical applications. For example, trials of a new opioid for use as an analgesic may suffer from the tendency of such pharmaceuticals to depress respiration, thereby increasing $CO_2$ levels, causing vasodilatation. This in turn can result in reduced BOLD signal changes during noxious stimuli, but it is then uncertain if the reduced signal is due to an increase in baseline blood flow or to a reduction in the neuronal response.

Hyperoxia has been shown to be effective in calibrating BOLD signal changes by calculating the maximum theoretical BOLD signal change for a given ROI (denoted by *M*).[1] A similar technique can also be employed to normalise BOLD changes between data obtained during differing baseline states. In this pilot study, subjects were imaged during a simple visual stimulus followed by mild hyperoxia, both pre and post caffeine ingestion, and the hyperoxia data was used to normalise the BOLD signal response to the visual stimuli. Caffeine is a nonselective adenosine receptor antagonist known to affect neurovascular coupling and to produce a pronounced vasoconstrictive effect[2].

**Theory & Methods**

Analogous to the derivation of the hypercapnia-calibrated model,[3] hyperoxia calibration makes use of the expression for BOLD signal change, as well as the expression for $R_2^*|_{dHb}$ derived by Boxerman *et al*.[4] The full hyperoxia model, which takes changes in CBF caused by the increased $PaO_2$ into account,[5] is given by[1]:

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]_v}{[dHb]_{v_0}}+\frac{CBF_0}{CBF}-1\right)^{\beta}\right)$$

where $M = TE \cdot A \cdot CBV_0 \cdot [dHb]_{v_0}^{\beta}$.

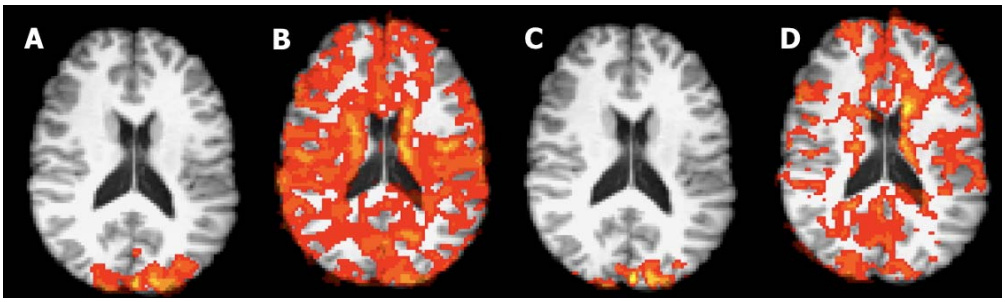
The BOLD activation during the visual task is expected to be different for the post-caffeine scans, however the neurovascular changes should also be manifested in a comparable change in the hyperoxia derived *M*-value. By representing the task activations as a fraction of *M*, rather than as a percentage change from baseline signal, the baseline physiological state should be eliminated as a confound.

Subjects (N=5), healthy, non-smoking volunteers, were scanned on a 3T Siemens TIM Trio, using a 12-channel receive head-coil. The sequence was a gradient echo EPI, TR=3s with 3mm isotropic voxels and 40 slices to give whole-brain coverage. Subjects were regular caffeine consumers, who were asked to abstain from caffeine for at least 4 hours before one scan (pre-caffeine), and were scanned 30 minutes after the normal consumption of a caffeinated beverage for the other scan (post-caffeine). The protocol lasted 10 minutes and 36 seconds, and consisted of 2 x 30-second on/off blocks of visual stimulus (8Hz alternating chequerboard pattern) and 2 x 2-minute on/off hyperoxia blocks. Oxygen was delivered via a 2-tube nasal cannula, which could deliver pure oxygen at a rate of 7 litres per minute while simultaneously sampling the inspired and expired gases. The delivery rate produced end-tidal $O_2$ values between 25 and 45% depending on subject breathing rate. Respiratory gas composition was measured using a Biopac MP150 with oxygen and carbon dioxide gas analyser units, at a rate of 25 Hz. The maximum end-tidal oxygen value at the end of each block was subsequently used to calculate *M*, along with the measured BOLD signal change during the hyperoxic epoch.

Analysis was performed using the FMRIB Software Library (FSL) package.[6] Activation was defined as the parameter estimate fitting with a Z statistic of greater than 2.3. All subjects were registered first to a T1-weighted 1mm isotropic structural image, and then to a MNI standard brain. Structurally defined ROI's were produced of the occipital lobe from the standard brain. This ROI was used to obtain a BOLD signal change value during both the visual and hyperoxia stimuli. The BOLD signal change during hyperoxia was used to calculate *M* for that region in each state.

**Results**

The relationship between caffeine and BOLD signal changes is complex.[2] Subjects showed a range of responses during the post-caffeine session in comparison to the pre-caffeine session. As previously reported[2] some subjects showed an increase in BOLD response, some a decrease and some showed no significant difference. The figure below shows the activated regions for one subject (#1) during the pre (A: visual & B: hyperoxia) and post (C: visual & D: hyperoxia) scans, exhibiting a decreased BOLD response. The table shows the numerical results for one subject (#5) in the occipital lobe ROI, also showing a decrease in BOLD activation. The mean relative change in BOLD signal pre and post caffeine (magnitude only) across all subjects was 25.2%, whereas the mean change in *M* fraction was 10.9%. The relation between the relative change in visual BOLD activation and the relative change in *M* value with caffeine was found to be $\Delta M\text{v\%} = 1.07*(\Delta\text{Bv\%}) + 0.05$, with an $R^2$=0.75, which indicates that *M* varies directly with BOLD signal change during altered baseline states.




| Condition | BOLD Visual | BOLD Hyperoxia | *ET O2* | *M*-vis | *M* Fraction |
|---|---|---|---|---|---|
| Pre-caffeine | 0.5114 | 0.9811 | 42% | 5.32 | 0.096 |
| Post-caffeine | 0.3115 | 0.3781 | 32.5% | 3.22 | 0.097 |
| Change | -39.09% | -61.46% | -22.6% | -39.47% | +1.04% |

**Discussion and Conclusions**

The hyperoxia normalisation of the BOLD response to the visual stimuli was used to produce a signal change expressed as a fraction of *M*, and this value was shown to have less variation between the pre and post caffeine states for all subjects. Despite changes in BOLD response on the order of 10-40%, the normalisation effectively reduced the effects of baseline neurovascular confounds. Hyperoxia may therefore be of use as a means of normalising functional MRI data during the presence of vasoactive compounds, which would otherwise be significant confounds in the interpretation of BOLD signal changes.

**References**

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