Impact of ASL and BOLD noise thresholds and duration of CO2 calibration on the estimates of calibrated BOLD

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INTRODUCTION: Blood oxygenation level dependent (BOLD) contrast [1] is now ubiquitous in monitoring brain function. In combination with additional measurement of blood flow it can also provide a window into metabolic changes [2, 3]. However, the calculations depend on assumptions such as the flow-volume relationship [4] and the scaling coefficient of the BOLD effect, defined as its theoretical maximum value "M" [5]. In this study we discuss potential bias in estimates of M when using isometabolic CO_2 challenges under experimental limitations of time and signal-to-noise ratio.

METHODS: We studied 10 subjects (7m+1f; plus two others whose data were rejected due to insufficient end tidal CO_2 change) in a Siemens Trio 3T MR scanner. An interlaced echoplanar BOLD and pulsed arterial spin-labelling (P-ASL) sequence was used to collect BOLD and Q2TIPS [6] volumes consisting of 5 slices of 64 × 64 voxels (4×4×6 mm^3). BOLD measurements had TR/TE=4.5s/32ms, and ASL experiments had TR/TE/TI=4.5s/23ms/1.4s. The experimental paradigm lasted a total of 49 minutes divided evenly into 7 epochs: three challenges of 3%, 4% and 5% CO_2 in air, each surrounded by baseline (normocapnia) periods. Temporal sinc-interpolation was performed on the set of ASL tag/control images to account for tag-control timing differences and to realign them with the BOLD measurements. Long-term trends were filtered out using spline interpolation between averages of baseline epochs collected during the 3 minute period before each challenge. We studied the sensitivity of the estimate of M in the whole group as a function of the rejection threshold based on data quality and as a function the CO_2 duration. We gradually increased the acceptance threshold (i.e. increased the rejection rate) so that the proportion of voxels deemed 'poor' and excluded from analysis ranged from 15% to 95%. The following methods of ROI mask selection were studied: mean value of the positive ASL effect (ASLm), ratio of ASLm to its variation in time (ASLm/SD); positive Z-ratio and SD of residual noise of the correlation model between BOLD (or ASL) and measured values of end tidal CO_2 (ASL or BOLD + glmZ or glmNoise respectively). We studied the additive (BOLD OR ASL) and multiplicative (BOLD AND ASL) combinations of some of these masks (Fig. 1&2, legend). To estimate the effect of a limited duration of CO_2 calibration we used the averages of progressive subsets of the data during each CO_2 epoch ranging from 30sec-7min, as well as the exponential asymptotic extrapolation of the data to infinite CO_2 epoch duration (studied at a 55% rejection threshold).

RESULTS:

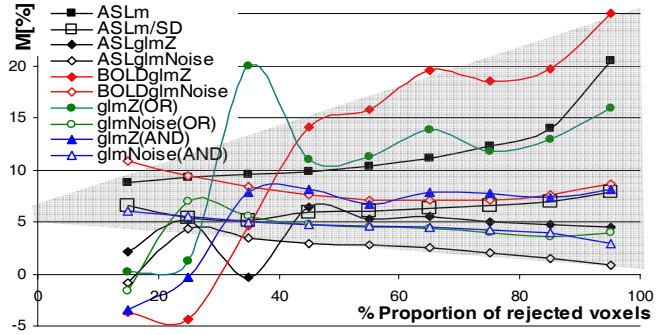

Figure 1) *Dependence of the estimates of M on the level of rejection of "low quality" voxels demonstrates the differing effects of M instability (particularly when rejection rate is <50%), and bias effects (grey cone) in masks based on BOLD and ASL signals. M is calculated from the averages of the last 3.5 minutes of the full 7 minute CO_2 challenge.*

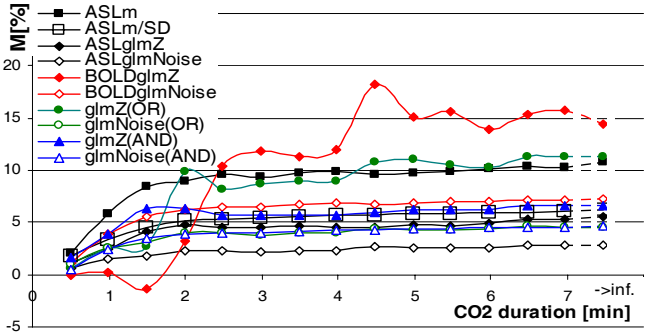

Figure 2) *Effect of the duration of CO_2 challenge on the estimate of M for a fixed 55% voxel rejection rate. Note that CO_2 epochs as long as 5 minutes are needed to achieve M values close to that approximated at infinity. The estimates obtained from challenges shorter than 3 minutes have generally lower values and vary significantly with time.*

DISCUSSION:

Changes in ASL and BOLD are not in general physically co-localized and their relationship is further complicated by their large difference in signal-to-noise ratio. Numerous methods for combining ASL and BOLD measurements can be proposed. Assuming the "worst case" scenario it can be argued that masks based on the ASL data alone should be used, resulting in stimulus-independent estimates like ASLm and ASLm/SD, and that the less noisy BOLD signal will always provide sufficient data quality for mask overlap. Alternatively, one can note that the meaningful M is needed mostly for those voxels that show responses for subsequent quantification. These voxels will have high Z score or low residual noise, at which BOLD excels, but at a cost of potentially biasing any results to venous voxels and thus to significantly larger estimates of M (Fig. 1: BOLDglmZ). We find that simple logical combinations are surprisingly dependent on the relative quality of their constituent signals, with "OR" combinations driven by more consistent BOLD responses, while "AND" combinations provide M estimates similar to ASL alone. For any descriptor of data quality the final result depends on the choice of threshold (the most consistent estimate being ASLm/SD, yielding variability in M of 13% across the tested rejection range, Fig. 1) and choosing an optimum is non-trivial as relationships vary and often are non-monotonic. The largest variability is visible at low levels of data rejection and seems to arise from incomplete rejection of noise. However, attempts to improve the stability of M estimates by increasing thresholds above 50% can significantly increase the amount of bias within the widening cone of estimates. Still further problems arise when the duration of the CO_2 challenge is shortened (in some studies to less than 1 minute), which we find produces a very significant underestimation in M. Fig. 2 demonstrates that any calculation of M produced by a CO_2 challenge of less than 3 minutes duration will be poorly estimated.

CONCLUSION: At least 3 minutes duration CO_2 calibration is needed to provide meaningful estimates of the value of M. Further, the estimate of M is significantly biased by the method used for the selection of mask voxels. Focal estimates of M based on the voxels showing a BOLD response can be several times larger than the value of M based on ASL, with the potential to severely confound estimates of metabolic changes in cerebral tissue.

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