Advanced fMRI: Techniques & Applications (Saturday, 30 May 2015)

Daniel Bulte **daniel.bulte@ndcn.ox.ac.uk**

Highlights

- BOLD & ASL fMRI can be calibrated to give $CMRO_2$ information
- Cerebral physiology can be quantified using combinations of sequences and isometabolic stimuli
- Signal models use combinations of BOLD, ASL, VSI and respiratory gas stimuli

FMRI USING CBF, CBV, & $CMRO_2$

Target Audience

- Clinicians and scientists seeking physiological and metabolic information about the brain both at rest and during tasks/stimulation.

Outcome/Objectives

- A broad understanding of the relevant imaging and measurement techniques used to quantify cerebral physiology
- An appreciation of the mathematical models used in physiological MRI
- A concept of the limitations and assumptions inherent in these techniques in regards to pathology

Purpose

BOLD fMRI signals are notoriously difficult to interpret as they are caused by an amalgam of changes in CBF, CBV and $CMRO_2$. This is further complicated by most fMRI experiments only producing "fractional changes" in BOLD, and not quantifying the changes in terms of the physiology. Over the last 20 years methods of disambiguating these effects have been developed based around BOLD signal models. In recent years new methods have emerged that seek to directly measure multiple aspects of the resting cerebrovascular physiology. These have evolved from earlier calibration techniques and tend to use combinations of multi-contrast pulse sequences and respiratory gas stimuli.

Methods

Blood Oxygenation Level Dependent (BOLD) functional MRI has revolutionised brain imaging. However, its strength lies in localising activity and it provides little or no information about the physiological changes that caused the signal, and no information about the underlying physiology in the brain at rest. Arterial Spin Labelling (ASL) has provided a means of either measuring relative changes in Cerebral Blood Flow (CBF), or of quantifying resting CBF, and thus is more easily interpreted in terms of the physiology. However as the real "activity" that is very often of interest is neuronal, the blood flow is still only a surrogate of the parameter of interest.

It is hypothesised that measurements of the cerebral metabolic rate of oxygen ($CMRO_2$) would provide a more direct interrogation of the neuronal activity, either at rest or during activation. The Davis model[1,2] relates the relative changes in BOLD signal during a task to changes in CBF and $CMRO_2$ via a calibration parameter

denoted by *M*, which depends on the total amount of deoxyhaemoglobin (dHb) at rest. The value of *M* corresponds to the maximum theoretical BOLD signal change that could be induced. As an increase in BOLD signal is caused by a reduction in deoxyhaemoglobin, if all of the dHb were removed to create a venous oxygen saturation of 100%, then the fractional difference in T2*-weighted signal between baseline and this state would be equal to *M*.

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CMR_{O2}}{CMR_{O2}|_0}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right)$$

The parameter α is the Grubb coefficient linking changes in CBF with changes in cerebral blood volume (CBV),[3] and β is a parameter that describes the sensitivity of the signal to magnetic field strength, tissue type, and mean vessel diameter.[4]

Results

The value of *M* can be determined by applying a stimulus that induces a BOLD signal change without affecting the $CMRO_2$. One way that has been used to do this is via a respiratory stimulus. This could be a hypercapnia stimulus (increased inspired fraction of carbon dioxide of approximately 5%) in conjunction with measuring the concomitant change in CBF using ASL. Another option is the use of a hyperoxic stimulus (increased fraction of inspired oxygen of approximately 50%) in conjunction with measuring the end-tidal oxygen levels.[5] Once regional values of *M* have been determined the above equation can be used with BOLD and ASL data from a functional task to calculate the relative change in $CMRO_2$ associated with that activity.

It was later realised that by combining both the hypercapnia and hyperoxia challenges into a single scan, the model could be expanded to provide quantitative information about multiple physiological parameters independently of any functional task.[6-8] It has been shown that the hypercapnia BOLD signal is sensitive to the product of CBV and $[dHb]_0$, whilst the hyperoxia BOLD signal is sensitive to CBV. Thus combining the 2 gas stimuli allows the resting deoxyhaemoglobin concentration to be determined.

By incorporating a multiple inversion time ASL sequence with the 2 gas stimuli, mathematical models can be employed to produce quantitative maps of CBF, CBV, arterial arrival time (AAT), oxygen extraction fraction (OEF), cerebrovascular reactivity (CVR), and $CMRO_2$. The CBV can be calculated from the BOLD response to hyperoxia,[9] while the CVR can be determined from either the BOLD or ASL response to hypercapnia. The $CMRO_2$ can be calculated from the resting CBF and the OEF. The total imaging time for this protocol is under 20 minutes, and it is recommended to be performed at 3 telsa using a dual-echo ASL-BOLD sequence. Pseudo-continuous ASL (pCASL) is the currently recommended sequence for quantifying CBF.[10] ASL imaging has a much lower signal to noise ration (SNR) than BOLD, and ASL data obtained at 1.5 tesla is generally too noisy to be reliably used with these models.

The data produced by these methods is comparable to oxygen 15 positron emission tomography (PET), but without the use of ionising radiation, or invasive arterial lines. Additional benefits of the MR method are a much lower cost, greater availability, and in a shorter scan time. Such an imaging method has great potential for use with stroke patients, vascular dementia patients, and a range of other neurological

pathologies, in addition to fields of neuroscience that would benefit from quantitative imaging.

As of 2014, second generation methods of obtaining quantitative physiological imaging using MRI are being developed. These use more sophisticated pulse sequences that add a spin echo acquisition to the 2 gradient echoes already collected. This extra data enables the calculation of the vessel size index (VSI), a parameter related to the mean vessel radius in the voxel, in addition to the OEF and CBV.[11] In this case it is only the vessels contributing to the BOLD signal via the gas challenges that contribute to the signal. These techniques make fewer assumptions about the physiology than the first generation models, and thus are more broadly applicable, enabling the imaging of greater degrees of pathophysiology.

Discussion

The Davis model implicitly assumes that subjects have a normoxic PaO_2 (are not hypoxic) and have a normal haematocrit (are not anaemic). It also implicitly assumes an arterial oxygen saturation (SaO_2) of 100%, and so all dHb, and thus BOLD signal, originating from metabolic activity. A mild hypercapnic stimulus (~4% CO_2) has been shown to induce a 0.5% increase in SaO_2 and 1.5% in SvO_2; hyperoxia (~50% O_2 inspired) leads to increases of 1% in SaO_2 and 2% in SvO_2. These results indicate that changes in oxygen saturation may occur across all vascular compartments, even in healthy subjects with high resting SaO_2. This suggests that changes in BOLD signal during gas-calibrated MRI scans have a small but significant arterial contribution.

Some researchers have reported a change in $CMRO_2$ during a hypercapnia challenge.[12] However, it must also be noted that there have been conflicting results that do not observe a change.[13] It may be possible to remove the requirement of a hypercapnia stimulus by determining the R_2' as a calibration step.[14] Whilst hypercapnia calibration seeks to emulate the physical removal of deoxyhaemoglobin from the blood, the aim of refocusing based calibration is to refocus the dephasing effect of deoxyhaemoglobin on the MR signal using a spin echo. However, it is not possible to refocus all of the effects that contribute to the BOLD signal and a scale factor is required to estimate the BOLD scaling parameter M.

Reductions in CBF during hyperoxia are often observed[15] and are primarily caused by mild hypocapnia,[16] which can be controlled for by preventing hyperventilation. There have also been reports of hyperoxia affecting the $CMRO_2$, and an increase in oxygen levels in the nasal sinuses or in the bore of the scanner can cause susceptibility and phase artefacts, and thus mild levels of hyperoxia combined with effective gas clearance methods are suggested.

Conclusion

Mathematical models of MRI signals can be used to calibrate or quantify imaging data. These can provide physiological information rather than simply localise activity during a functional task. More sophisticated pulse sequences and additional physiological stimuli, such as altering respiratory gas composition, can produce data for BOLD signal models that enable the calculation of multiple physiological parameters including oxygen extraction fraction and cerebral metabolic rate of oxygen. Due to the reliance of most models on CBF data, ASL data is usually required, and thus 3 tesla MRI systems with high-end head coils are recommended.

References

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