Bayesian and lagged general linear modelling strategies in breath-hold induced cerebrovascular reactivity mapping with multi-echo BOLD fMRI

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Synopsis

Cerebrovascular reactivity (CVR), the ability of blood vessels to dilate and constrict in response to a vasoactive stimulus, is an important indicator of cerebrovascular health and can be estimated using BOLD functional MRI. In this work, we evaluated a novel variational Bayesian method for mapping CVR dynamics which yielded similar CVR results and reproducibility to a time-shifted, "lagged" general linear model approach, and uncovered the need for more research into negative CVR. This novel approach is more time efficient and has the potential to improve CVR mapping by incorporating non-linear modelling and physiologically meaningful information (in the form of priors).

Summary of Main Findings

A novel variational Bayesian method for mapping cerebrovascular reactivity (CVR) dynamics yielded similar results and reproducibility to a time-shifted GLM approach, and uncovered the need for more research into the implications of negative CVR.

Introduction

Cerebrovascular reactivity (CVR) reflects the intrinsic mechanism of blood vessels to alter their calibre in response to a vasoactive stimulus (e.g. a change in arterial CO_2 content). Functional magnetic resonance imaging (fMRI) based on blood oxygen level-dependent (BOLD) contrast acquired during breath-hold (BH) tasks is a non-invasive, robust method to derive CVR maps[1], being increasingly used to assess various pathologies, including cerebrovascular diseases[2], brain tumours[3], and neurodegenerative disorders[4].

CVR is commonly quantified by its amplitude changes, but temporal features might provide information of interest. One way of retrieving both the temporal and amplitude information is by using a lagged general linear model with time-shifted regressors (lGLM)[5]. Recently, a variational Bayesian (VB) approach has been applied to CVR, allowing for non-linear model fitting and the incorporation of priors[6]. In this study, we evaluate the performance of these two methods on multi-echo BOLD fMRI data, acquired in ten subjects performing a BH task during ten repeated sessions[7], to obtain subject-specific CVR and haemodynamic delay estimates and their corresponding reproducibility metrics.

Methods

Multi-echo BOLD fMRI data was acquired in ten subjects performing a BH task during ten sessions (3T Siemens PrismaFit; 340 scans, TR=1.5s, TEs=10.6/28.69/46.78/64.87/82.96ms, FA=70°, multiband=4, GRAPPA=2 with gradient echo reference scan, 52 slices with interleaved acquisition, Partial Fourier=6/8, voxel size=2.4×2.4×3mm^3)[7]. The task involved eight repetitions of four paced breaths (6s each), a 20s BH, 3s exhalation, followed by a recovery period (11s without pacing)[8]. Partial pressure of end-tidal CO_2 ($PETCO_2$) levels were acquired throughout[1]. Four subjects were excluded due to poor BH performance.

MRI data processing was performed using AFNI[9], FSL[10] and ANTS[11], including multi-echo T2*-weighted combination[12], followed by nuisance regression of up to fourth-order Legendre polynomials, parameter realignment, and temporal derivatives. The $PETCO_2$ time-courses were processed and the end-tidal peaks selected (Python 3.6.7).

The CVR toolbox in Quantiphyse[13] was used for the lGLM and VB analyses to estimate the CVR amplitude and delay maps[6] for each session/subject. To account for measurement delay, Quantiphyse applied a bulk shift to each $PETCO_2$ trace to maximise its cross-correlation with the average whole-brain fMRI signal. We established a window for the candidate delays of ±8s from the bulk shift with a 1s timestep for the lGLM approach, whereas this information is not required in the VB approach.

The estimated CVR maps were scaled to BOLD change over the change in $PETCO_2$ (%BOLD/mmHg). The delay maps were centred with respect to the session-specific average delay within the brain's voxels.

To compare the results, the maps were transformed to the MNI152 template[14] (nearest neighbour interpolation[14]). A linear mixed effects (LME) model was then applied voxel-wise,

taking into account variability within and across subjects[15]. An intraclass correlation coefficient (ICC(2,1)) was also computed voxel-wise for the standardised CVR and delay maps using AFNI's 3dICC to assess each method's reproducibility[16], considering 6 subjects and 10 sessions per subject.

Results and Discussion

The CVR amplitude and delay maps derived for each session for one representative subject are presented in Figure 1 and Figure 2, respectively, for each method. The CVR values in GM are highly comparable between methods and to previously reported values[7]. Notably, the lGLM approach reports negative CVR values, mostly in WM and ventricles CSF voxels, while the VB does not due to its non-negative prior on CVR amplitude as displayed in Figure 3. This negative CVR might originate from inaccurate modelling in noisy voxels with reduced CVR-related changes, the effect of "vascular steal", and/or CSF flow and volume changes[17].

Figure 4 highlights statistically significant differences between methods in specific regions (e.g., WM and CSF). No significant differences were observed across grey matter. The high ICC scores (>0.6) in the CVR amplitude maps (Figure 5) indicate a high reproducibility with higher inter-subject variability than intra-subject variability in both methods. These ICC scores are lower than in a previous work[7], which applied ME-ICA denoising, simultaneous modelling and considered a finer timestep for the lGLM approach, which warrants further investigation on the effect of these preprocessing and modelling choices, particularly for the VB approach.

The lGLM approach was found to be less robust to noisy $PETCO_2$ data when the automated bulk shift estimation is inaccurate since no shifting outside of the defined delay bounds is considered. Furthermore, the VB method can be more time efficient at scale as it fits the CVR amplitude and delay simultaneously, while the lGLM assesses the CVR amplitude for multiple delay values. These strategies offer robust quantification of CVR and can be particularly relevant for assessing patients with diseases where cerebral hemodynamics might be compromised.

Conclusion

lGLM and VB modelling strategies provide robust CVR amplitude and delay maps for breath-hold BOLD fMRI data. Due to the priors incorporated in Bayesian regression, the VB analysis may provide a more accurate functional assessment of BOLD signals than the lGLM approach and may perform faster when high temporal resolution in the delay maps is necessary. More research is still required to better understand the physiology and implications behind negative CVR in BOLD fMRI. Future work will include testing different VB priors, including negative values.

FIGURES

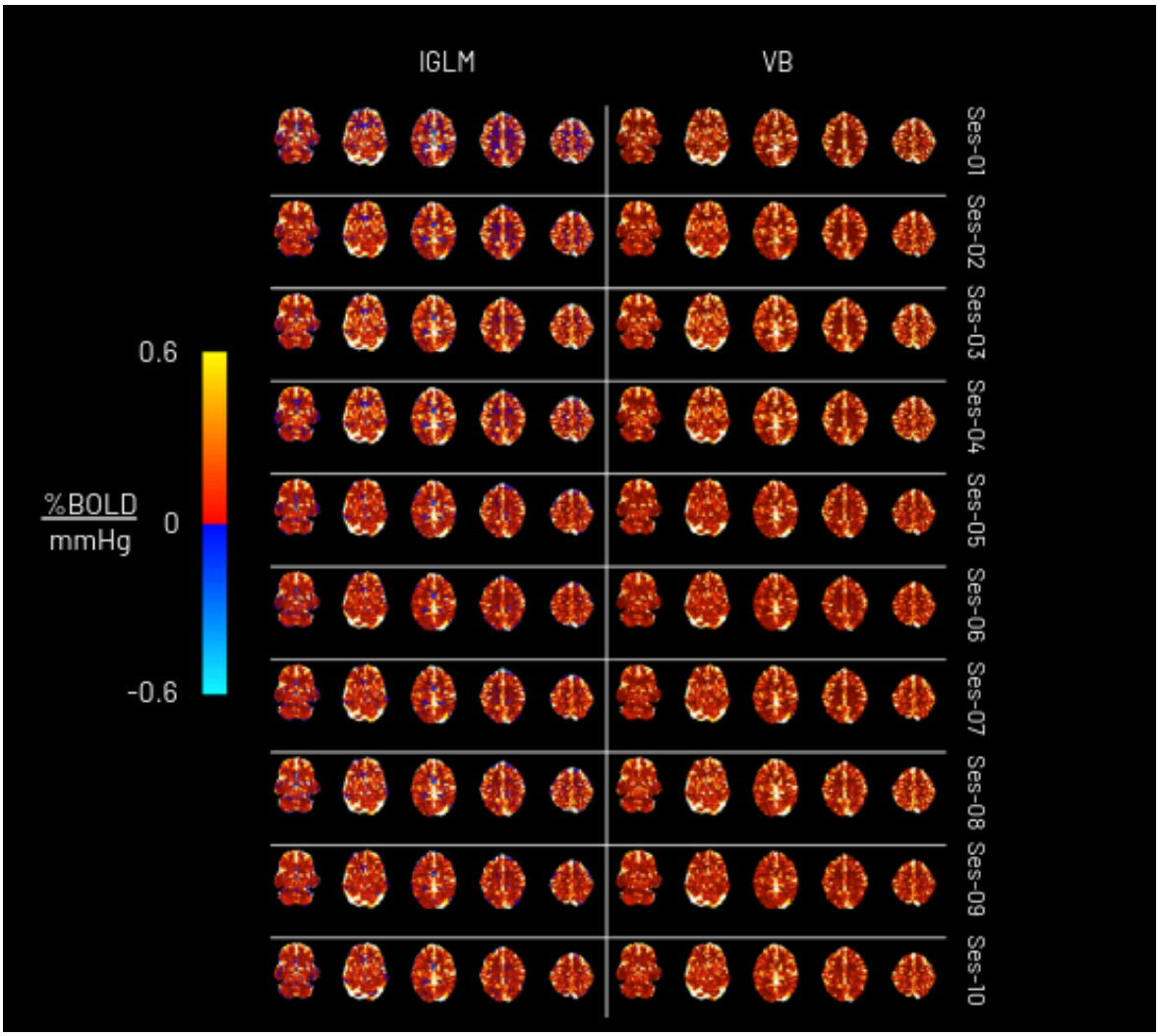

Figure 1: CVR amplitude maps obtained using the lagged-GLM (lGLM) and variational Bayesian (VB) analyses for all the sessions of a representative subject (subject 002). Each row represents a session.

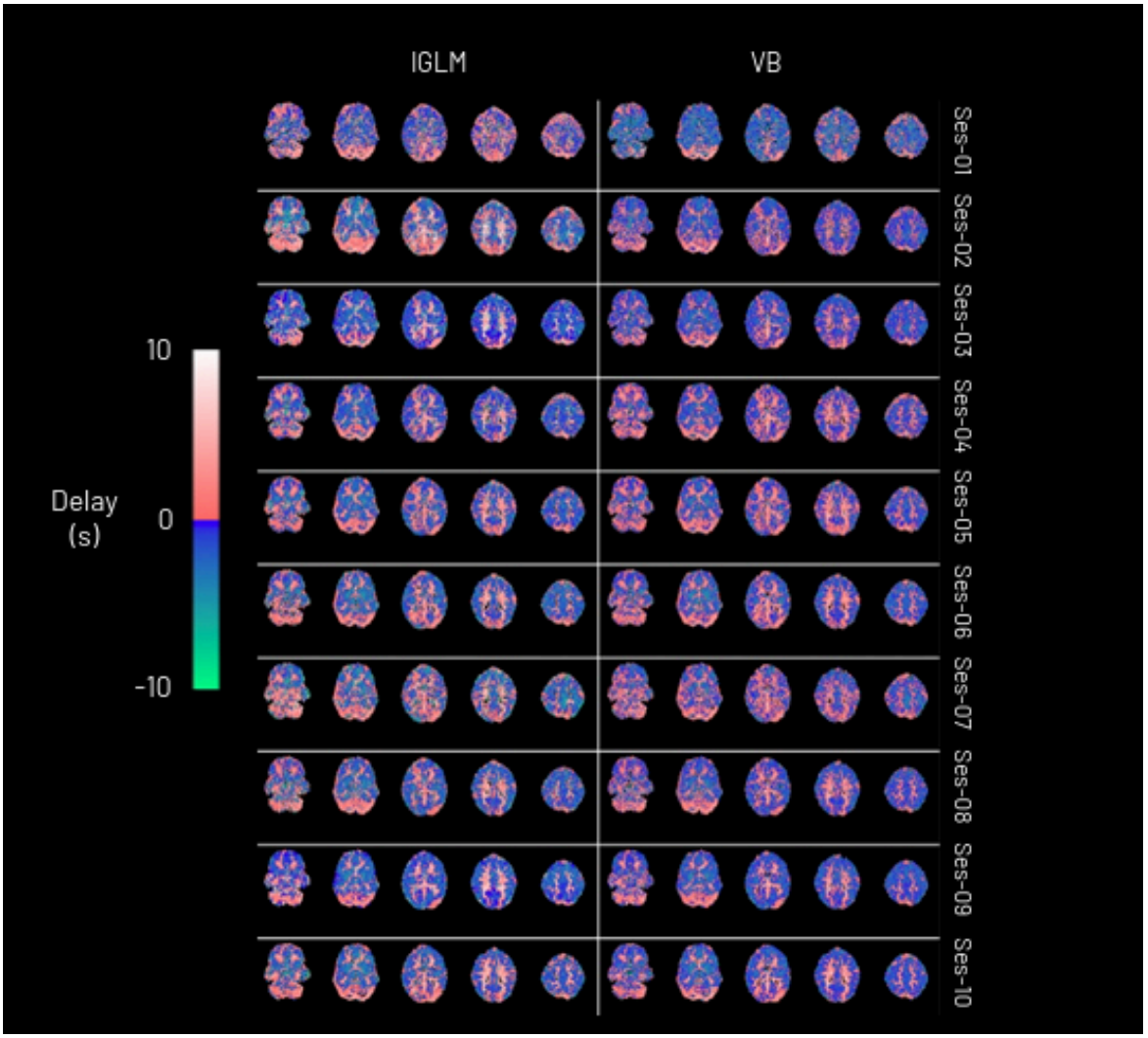

Figure 2: CVR haemodynamic delay maps obtained using the lagged-GLM (lGLM) and variational Bayesian (VB) analyses for all the sessions of a representative subject (subject 002). Each row represents a session.

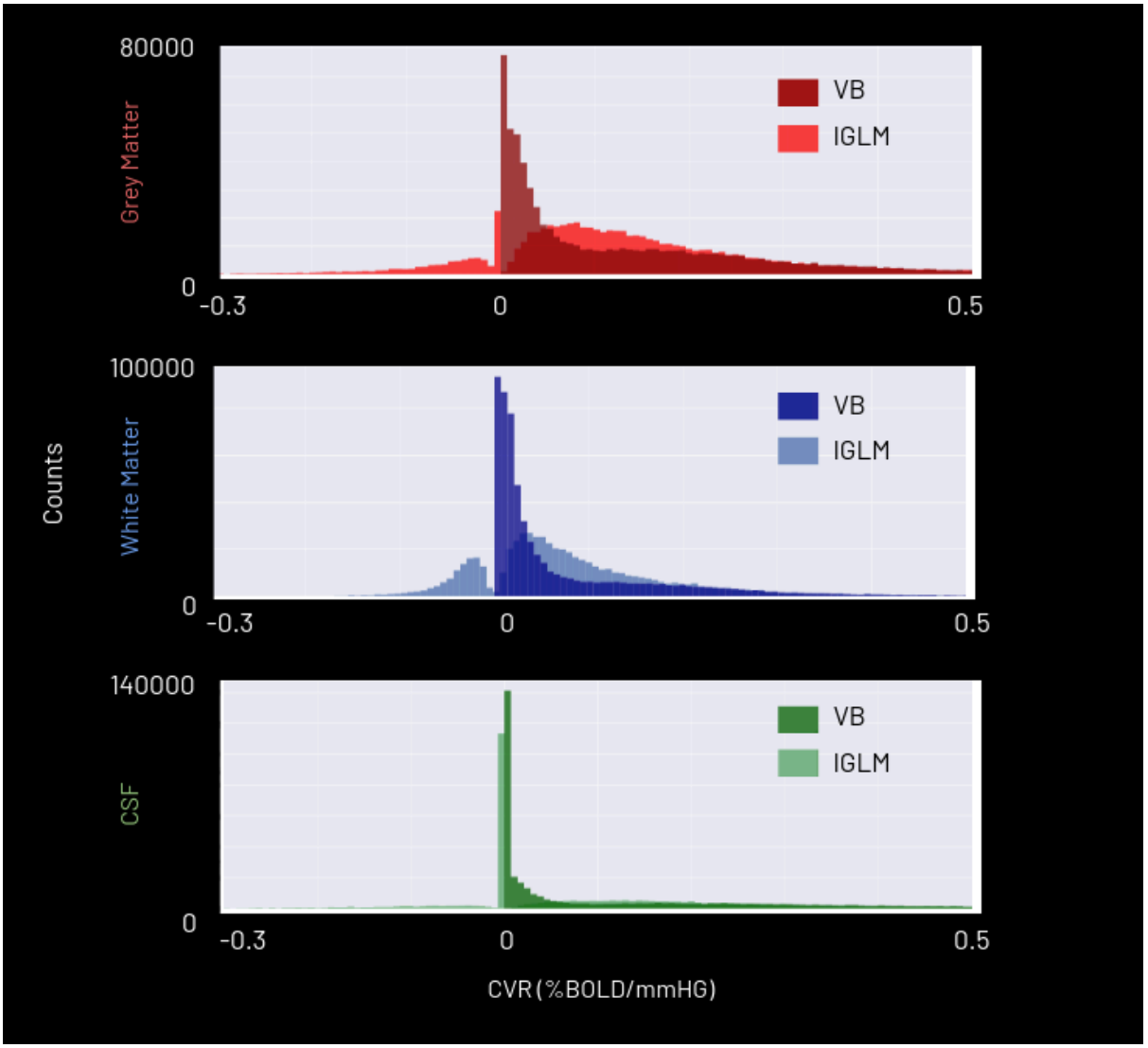

Figure 3: Histograms of a representative subject and session using the lagged-GLM (lGLM) and variational Bayesian (VB) analyses in grey matter (top), white matter (centre), and cerebral spinal fluid (CSF; bottom). The VB histograms are presented in darker colours and the lGLM are lighter. Similar histograms were observed for the rest of sessions and subjects.

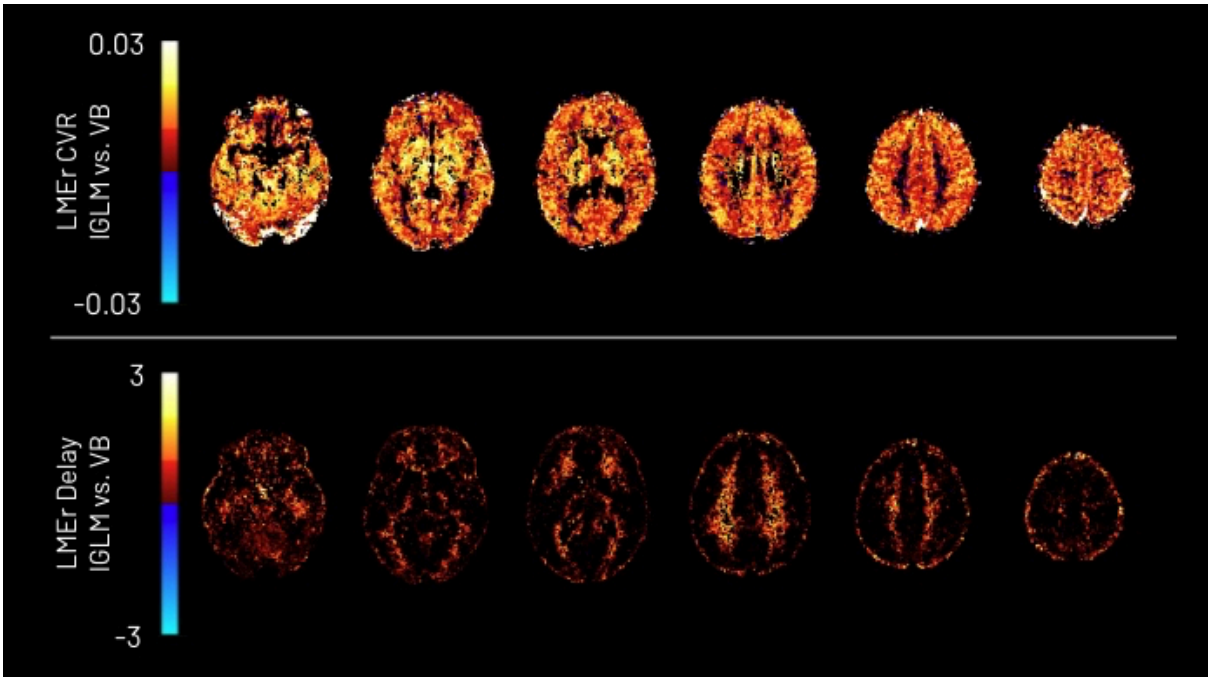

Figure 4: Revised linear mixed-effects (LMEr) pairwise comparison between the lagged-GLM (lGLM) and variational Bayesian (VB) analyses. It should be noted that the range of -0.03 to 0.03 is much smaller than the range of CVR values which is -0.6 to 0.6.

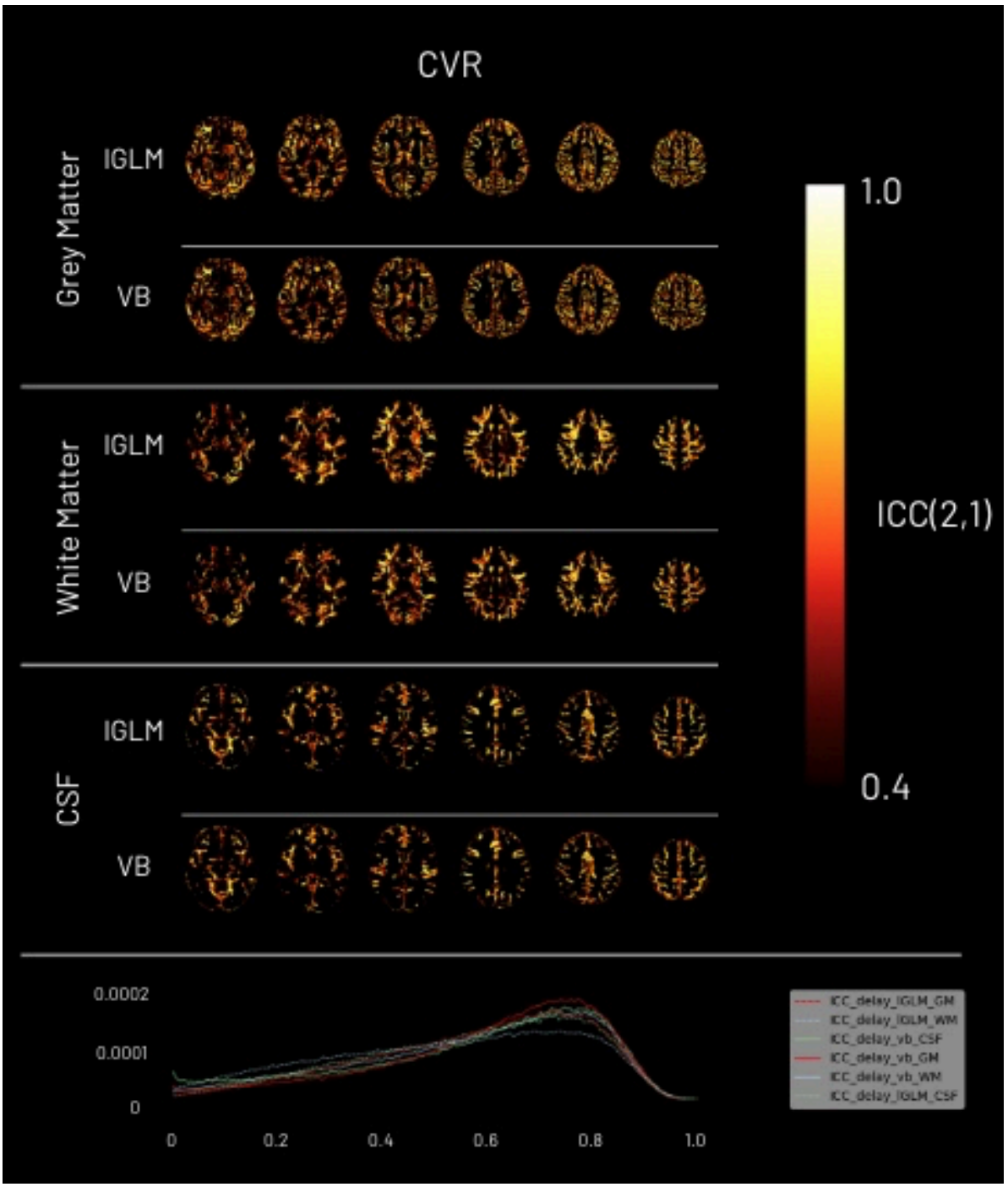

Figure 5: Intraclass correlation coefficient ICC(2,1) maps of CVR for the lagged-GLM (lGLM) and variational Bayesian (VB) analyses in grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF). The maps are thresholded at 0.4 since scores lower than it indicate poor reliability. An ICC score lower than 0.6 is considered fair, lower than 0.75 good, and equal or higher than 0.75 excellent. The bottom row depicts the GM, WM, and CSF distributions of ICC scores across voxels.

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