FAILURE OF THE "STANDARD" FMRI ANALYSIS IN THE VISUAL CORTEX USING A SMOOTH VISUAL STIMULUS

David Provencher[1], Andreas Bartels[2], Yves Bérubé-Lauzière[3,4], and Kevin Whittingstall[4,5]

[1]*Department of Nuclear Medicine and Radiobiology, Université de Sherbrooke, Sherbrooke, QC, Canada,* [2]*Werner Reichardt Centre for Integrative Neuroscience, Tübingen, Germany,* [3]*Department of Electrical and Computer Engineering, Université de Sherbrooke, Sherbrooke, QC, Canada,* [4]*Centre d'imagerie moléculaire de Sherbrooke (CIMS), Université de Sherbrooke, Sherbrooke, QC, Canada,* [5]*Department of Diagnostic Radiology, Université de Sherbrooke, Sherbrooke, QC, Canada*

INTENDED AUDIENCE: The fMRI community, more specifically scientists computing activation maps via convolution of the stimulation paradigm waveform (SPW, e.g. a boxcar function) with the canonical hemodynamic response function (HRF).

PURPOSE: Typical task-based fMRI studies model neurovascular coupling (NVC) using the canonical HRF, implicitly assuming that 1) neural activity follows the SPW and that 2) the HRF is constant across individuals and brain regions. However, neural activity is seldom measured, while the HRF has generally been characterized during stimuli with sharp transitions and has shown variation across subjects and regions.[1-3] Better understanding in which conditions the above assumptions hold is necessary, since many applications, such as neuroscience research and surgical planning, require accurate and reliable fMRI activation maps. It is currently unknown whether the "standard" fMRI analysis is appropriate when using stimuli with slow transitions and the present study aims to address this.

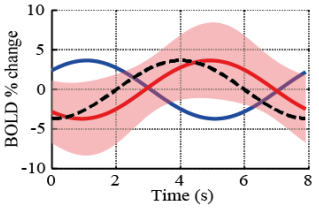

Fig. 1*: *Red*: Average BOLD response in the V1 ROI of a representative subject (S1). *Blue*: BOLD model obtained with the "standard" fMRI analysis. *Black*: SPW.

METHODS: We acquired sequential EEG (63 electrodes; 256 Hz; 144 trials) and fMRI (3T; EPI: 64x64, 26 slices, 3x3x4 mm^2 voxels, TR/TE = 1800/38 ms; 56 trials) data in 5 healthy subjects viewing outward flowing random dots with sinusoidally varying contrast over 8 s. EEG preprocessing was performed using EEGLAB [4] and consisted in bad channel removal, band-pass filtering (0.1-45 Hz) and independent component analysis denoising.[5] Preprocessing of fMRI, performed using AFNI,[6] included slice-time correction, motion-correction, skull stripping, spatial smoothing (4.8 mm), band-pass filtering (0.01-0.15 Hz) and percent-change computation. Anatomical ROIs for V1, V2, V5+/MT+ and the whole occipital cortex were obtained using FreeSurfer.[7] Both EEG and fMRI signals were resampled to 10 Hz and averaged across trials. To extract the component of neural activity present in the EEG data, we computed the power modulation in decibels (dB) in the frequency band displaying the strongest modulation time-locked with the stimulus using a time-frequency decomposition and Hilbert's transform on the occipital EEG (electrodes O_z, O_1, O_2, PO_z, PO_3, PO_4, PO_7 and PO_8). To better estimate hemodynamic delay, blood oxygen level-dependent (BOLD) responses in the occipital cortex ROI were separated in 6 clusters of similar timecourses using a K-means clustering algorithm. For each subject, 8-second long HRFs were then computed at a resolution of 1 Hz based on the EEG power modulation and the average BOLD timecourses in each cluster using linear deconvolution.

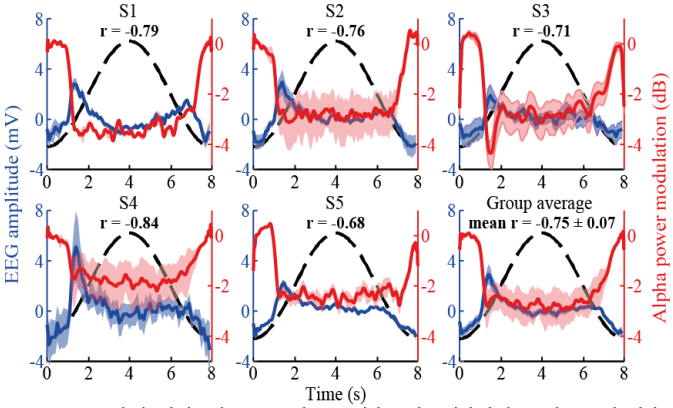

Fig. 2*: EEG-derived signals averaged over trials and occipital electrodes. *Red*: Alpha power modulation. *Blue*: EEG amplitude. *Black*: SPW. Correlation coefficients (r) between the alpha power modulation and SPW curves are indicated.

*** Shaded areas represent 1 standard deviation**

RESULTS: We found that the BOLD responses were nearly sinusoidal with the same period as the stimulus (**Fig. 1**), but that delays varied relative to the SPW across brain regions. Typical latencies of 1-3 s were observed, considerably shorter than the 5-6 s latency of the canonical HRF peak, translating to evident discrepancies between the modeled and measured BOLD. Moreover, although the evoked neural activity (i.e. alpha band power modulation) correlated well with the SPW, it displayed a boxcar-like, rather than sinusoidal, shape (**Fig. 2**). The BOLD peak latency varied across voxels, with no clear single peak timing dominating in either ROI (**Fig. 3**). The cluster-averaged BOLD timecourses were similar across subjects. While inter-subject variability was evident, the associated spatial maps were coarsely symmetrical about the midline and mostly displayed smooth peak latency transitions between neighboring voxels. Finally, deconvolved HRFs were approximately sinusoidal with a period of 8 s, contrasting with the canonical HRF (**Fig. 4**).

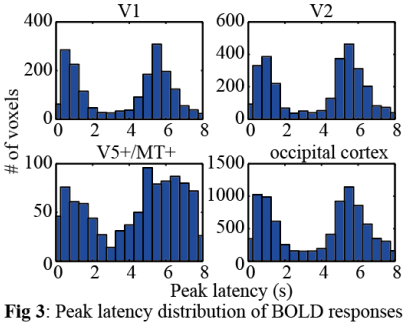

Fig 3: Peak latency distribution of BOLD responses

DISCUSSION: We investigated the causes of the disparity between measured and modeled BOLD by comparing the evoked neural activity with the SPW and by estimating HRFs through deconvolution of EEG alpha power modulation and clustered BOLD timecourses. Results suggest that 1) the underlying neural activity does not follow the SPW, contrary to a common assumption in the fMRI literature, and that 2) the canonical HRF, with its fixed 5-6 s peak latency, cannot alone account for the wide range of hemodynamic delays observed in either V1, V2, V5+/MT+ or the whole occipital cortex. Convolving the SPW with the canonical HRF is therefore not an adequate modeling approach for all stimulus types. The obtained sinusoidal shape of deconvolved HRFs is coherent with the boxcar-like behavior of the alpha power modulation and the sinusoidal BOLD timecourses. HRF duration was ultimately limited by acquisition parameters, therefore in-depth interpretation of HRF shape is left for future study. However, it remains that this duration was sufficient to capture a complete cycle of the sinusoidal HRFs and that the use of K-means clustering allowed estimating HRFs corresponding to distinct BOLD dynamics.

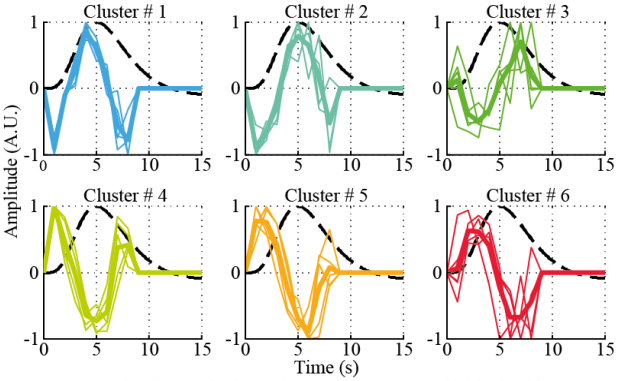

Fig 4: Deconvolved HRFs in the 6 clusters. *Thin lines*: Individual subjects. *Bold lines*: Subject average. *Black*: canonical HRF.

CONCLUSION: The main finding of this study is that the BOLD response to a slowly changing visual stimulus cannot be accurately modeled by the typical BOLD modeling approach. We showed that common assumptions in the "standard" fMRI analysis are not necessarily applicable for all stimulation paradigms or all brain regions. First, we found that BOLD response times varied considerably within the occipital cortex, with some of the responses being much faster than predicted by the canonical HRF. Second, we found that the waveform of the EEG-derived neural signal differed considerably from the SPW, even though both were well correlated. Our findings imply that it may be good practice to substitute the SPW for neural activity in the absence of neural measurements, but that actual neural activity waveforms may differ considerably. Third, we demonstrated that actual HRFs can differ substantially from the commonly assumed canonical model. Finally, the methods developed in this study show potential for HRF variability characterization using EEG-fMRI.

REFERENCES: [1] Aguirre *et al*., NeuroImage, 1995. [2] Gonzales-Castillo *et al*., PNAS, 2012. [3] Handwerker *et al*., NeuroImage, 2004. [4] Delorme & Makeig, J Neurosci Methods, 2004. [5] Whittingstall *et al*., Magn Reson Imag, 2010. [6] Cox., Comput Biomed Res, 1996. [7] Reuter *et al*., NeuroImage, 2012.