**BOLD hemodynamic response function changes as a function of both brain state and brain region.**

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Introduction :

Blood oxygen level dependent functional magnetic resonance imaging (BOLD FMRI) has become the most widely used imaging modality for investigating human brain activity, and changes in the BOLD signal are thought to reflect changes in underlying neural activity. However, the precise relationship between neural activity and BOLD is still unknown.

Typically a hemodynamic response function (HRF), which assumes a linear relationship between neural activity and BOLD [1], is used to relate neural activity to BOLD. Neural activity is convolved with the HRF, giving the BOLD signal. In most instances, the HRF is assumed to be the same in all brain areas and states. For example, when computing resting state FMRI connectivity, the assumption is that different brain regions all possess the same HRF, making it possible to correlate BOLD signals from different brain areas. Similarly, in studies of dynamic functional connectivity, the HRF is assumed to not change over time, and observed changes in FMRI connectivity patterns are assumed to indicate changes in patterns of network activity.

Using simultaneous EEG-FMRI, we investigated the assumption that the HRF does is constant across brain region and time, by observing simultaneous alpha-BOLD and gamma-BOLD coupling in different brain states and regions.

Methods :

Simultaneous EEG-FMRI in a 3T Philips Ingenia, 9 healthy subjects recruited from University of Sherbrooke (4 female), EEG sampling 64 channel Brainvision EEG cap, FMRI TR=0.693, voxel size = 3.75mm, image size 64x64x33mm isotropic, multiband 3.

Four separate brain states were investigated: retinotopic mapping, resting state, event-related stimulus, and continuous stimulus (movie). With the exception of resting state (eyes closed), subjects were required to fixate a red crosshair for the duration of the scan, each scan lasted 8.5 minutes.

EEG and FMRI were denoised using temporal and spatial ICA respectively, removing noise components (motion, heart beat, ventricles, white matter, eye blinks, etc) by visual inspection. Clean EEG signals were source-localized (250Hz, 8mm isotropic) using precise electrode locations [2] and head model [3]. Power was computed in each source voxel using multi-taper time-frequency analysis. Clean FMRI signals were bandpass filtered [4] (0.01-0.5Hz) and correlated on a per-voxel basis with source localized EEG power time series. A preprocessing flow chart can be seen in Figure 1A, and EEG data quality control in Figure 1B (comparing EEG acquired inside and outside the scanning environment in response to visual stimulus).

Voxel-based correlation of EEG and BOLD was performed two ways 1) convolving EEG power with HRF [1] and then correlating with BOLD, resulting in an EEG-BOLD coupling spectrum from 0-100Hz in each voxel, or 2) cross correlation of EEG power with BOLD, resulting in an EEG-BOLD coupling time-frequency matrix in each voxel.

Results :

A general pattern of positive gamma-BOLD correlations and negative alpha/beta-BOLD correlations is consistent across brain states (Figure 2A).

EEG-BOLD coupling differs across regions: when comparing alpha-BOLD coupling in the default mode network (DMN) and primary visual cortex (PVC), HRF-convolved alpha power correlated more strongly with BOLD in PVC than in DMN (Figure 2B, p=0.005).

EEG-BOLD coupling differs across states: when comparing alpha-BOLD and gamma-BOLD coupling in PVC across states, the retinotopic mapping experiment trended towards stronger coupling for both frequency bands as compared to resting state (Figure 2C, p=0.08, p=0.11).

Cross correlation analysis reveals non-canonical hemodynamic response function which varies regionally: averaging across all brain states and regions revealed biphasic coupling in the 10-20Hz frequency range with positive coupling at 0-4s time lag, and negative coupling at 5-10s time lag (Figure 3A). PVC had negative alpha-BOLD coupling and positive gamma-BOLD coupling at canonical time lag (6sec) (Figure 3B, Figure 3D), while DMN had positive alpha-BOLD coupling at non-canonical time lag (3s) (Figure 3C, Figure 3E).

Discussion :

In accordance with previous work [5], our cross-correlation analysis revealed reliable BOLD-EEG alpha/beta coupling at 6-8s time lag. However, the HRF varies as a function of both brain state and area, and the fixed hemodynamic delay of 6 seconds does not hold for all areas. Furthermore, in some areas such as DMN, alpha-BOLD coupling is positive, with a shorter time lag, suggesting that changes in DMN activity are linked to alpha synchronization rather than desynchronization [6].

The fact that coupling varies regionally means that BOLD signal connectivity measured across different brain areas [7] must be interpreted with caution. The fact that coupling varies as a function of brain state suggests that dynamic changes in functional connectivity[8] may be partly due to changes in coupling, rather than changes in connectivity across areas.

Conclusion: The relationship between EEG power and BOLD is state and region dependent. More work is necessary to understand the neural basis for BOLD signals, and the extent to which connectivity measures depend on choice of HRF.