Retrieving the hemodynamic response function in resting state fMRI: methodology and applications

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**Background:** Retrieving the hemodynamic response function (HRF) in fMRI data is important for several reasons. Apart from its use as a physiological biomarker, HRF can act as a confounder in connectivity studies. In task-based fMRI is relatively straightforward to retrieve the HRF since its onset time is known. This is not the case for resting state acquisitions. We present a procedure to retrieve the hemodynamic response function from resting state (RS) fMRI data. The fundamentals of the procedure are further validated by a simulation and with ASL data. We then present the modifications to the shape of the HRF at rest when opening and closing the eyes using a simultaneous EEG-fMRI dataset. Finally the modulation of this RS-HRF with propofol anesthesia is presented.

**Methods:** The procedure starts from the assumption that resting-state brain dynamics can be driven by spontaneous events, which are retrieved by setting a threshold on the normalized BOLD signal. A linear time invariant (LTI) system is used to model the relationship between spontaneous neural events and the BOLD response. Once the events have been collected, a GLM is fitted using the delay between event and BOLD peak as a free parameter. The HRF is retrieved both with the canonical model with derivatives (canon2dd) or as a Finite Impulse Response (FIR). Simulated HRFs are used as the ground truth for simulations. We employ a public dataset to explore the relationship between baseline CBF and HRF. We investigate the electrophysiological basis of the HRF and its coupling to electrical brain activity with simultaneously recorded EEG and fMRI data acquired at 7T.

**Results:** Starting from lower but still realistic SNR values, the fit between simulated and retrieved HRF is stable and accurate. A correlation analysis across voxels in each subnetwork showed a striking spatial overlap between CBF and HRF response height (PSC, baseline). Less differences are observed in other HRF parameters, probably due to the sampling rate. A positive correlation between BOLD and canonical HRF convolved alpha power was observed in the thalamus, and a negative one in the Occipital Lobe. We observe opposite patterns of HRF shapes between the thalamus and occipital cortex under the two conditions, consistent with the correlation and anti-correlation between the alpha power spectrum and BOLD signal in thalamic and occipital cortex.

**Conclusions:** The feasibility and effectiveness of an algorithm aimed to retrieve the HRF at rest is overall confirmed by simulation data, and evidence from vascular flow and electrophysiology. Additionally, functional modifications to the HRF shape are consistent with evidence previously reported using different methodologies.