Intrinsic connectivity network activity revealed by the independent modelling of the primary and post-stimulus components of the BOLD response

Karen J Mullinger[1], Stephen D Mayhew[2], Andrew P Bagshaw[2], Richard Bowtell[1], and Susan T Francis[1]

[1]*SPMMRC, School of Physics and Astronomy, University of Nottingham, Nottingham, United Kingdom,* [2]*BUIC, School of Psychology, University of Birmingham, Birmingham, United Kingdom*

Introduction: Recent evidence suggests that the BOLD post-stimulus response has a distinct neuronal origin [1]. Its polarity (undershoot or overshoot) can be predicted by the post-stimulus power (PSP) of mu-frequency (8-13Hz) EEG activity [2] and is independent of the polarity of the primary BOLD response. Thus, conventional modelling of BOLD responses with an assumed canonical HRF cannot fully represent the trial-by-trial variability that occurs in both primary and post-stimulus phases of the response.

Recently, we showed that post-stimulus BOLD responses in primary sensorimotor cortex (S1/M1) are modulated bilaterally by EEG-mu PSP in regions showing both positive (contralateral) and negative (ipsilateral) primary BOLD responses [2], suggesting the action of a consistent post-stimulus mechanism across the whole S1/M1 network. Intrinsic connectivity networks (ICNs) of functionally related regions exist during both stimulation and rest [3], however little is known about the changes in their activity in the transition between task and rest periods. Simultaneous EEG-BOLD measures provide an interesting new method to study this transition. Expanding on our prior work showing mu PSP indexes the modulation of both positive and negative BOLD responses during- and post-stimulation [2], here we:

A) create a model to describe S1/M1 BOLD responses which features a sustained primary response, and separable components characterising the amplitudes during the primary and post stimulus phases, each informed by mu PSP (Figure 1). This model can be applied to both positive and negative BOLD response regions and allows the separation of areas involved in BOLD modulation both during and after stimulation.

B) use this new model to create a General Linear Model (GLM) so as to identify the ICNs involved in the mu PSP modulations occurring a) during and b) post median nerve stimulation.

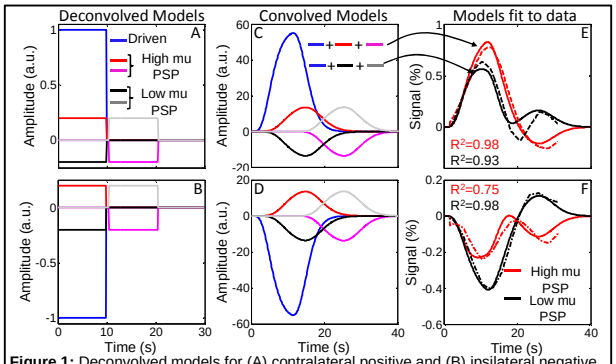

Figure 1: Deconvolved models for (A) contralateral positive and (B) ipsilateral negative primary BOLD response, with corresponding models (C&D) and fitted responses (solid lines, E&F) to BOLD HRs acquired from S1/M1 (dashed lines, E&F) .

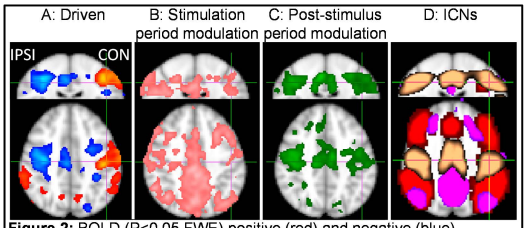

Figure 2: BOLD (P<0.05 FWE) positive (red) and negative (blue) correlations with regressor i) (A), BOLD positive correlations with regressor ii) (B) and regressor iii) (C). D: DAN (red), DMN (purple), S1/M1 (brown) networks obtained from independent component analysis.

Methods: fMRI and EEG data were acquired simultaneously using a Philips Achieva 3T MR scanner and a 64-channel EEG system (Brain Products). A FAIR Double Acquisition Background Suppression (DABS) [4] sequence was used for simultaneous acquisition of background suppressed ASL and BOLD data covering S1/M1 (TR=2.6s, TE=13/33ms [ASL/BOLD]), label delay=1400ms, background suppression times of T_{BGS1}/T_{BGS2}=340/560ms, 3x3x5mm^3 voxels, 10 slices). Median nerve stimulation (MNS, 2Hz, Digitimer DS7A) was applied to the right wrist of 18 right-handed subjects (age=27±3yrs) at each individual's motor threshold. Data were recorded over 40 trials (10s/20s MNS/rest).

Analysis: EEG and fMRI data were pre-processed using conventional methods, and the BOLD data alone were used in the fMRI analysis with ASL data used in other analyses [2]. Five subjects were excluded due to excessive movement or poor EEG data quality.

EEG: For each subject virtual electrode timecourses of EEG activity were extracted using a beamformer [5] in contralateral S1/M1 and mean mu PSP (10.5-20s) calculated for each trial [2]. For each subject, these values were mean corrected and then trials were sorted into low (0-25%), and high (75-100%) quartiles.

fMRI: A) Creating a model to best-fit the data: (I) The group contralateral (positive)/ipsilateral (negative) S1/M1 BOLD regions responding to MNS were identified using a conventional GLM analysis (SPM5) with a boxcar regressor of the stimulation period convolved with the canonical HRF, and a fixed-effects analysis performed (P<0.05, FWE corrected). (II) For each subject, single-trial HRs were extracted from these S1/M1 regions and converted to percent change, sorted into quartiles according to mu PSP, and averaged to generate quartile HRs. These quartile HRs were then averaged across subjects (Figure 1E&F). (III) A model was then formed to optimally describe these high and low quartile HRs in terms of amplitude modulations and peak latency shifts between quartiles. The model comprised three components: *i) driven, constant amplitude* during all stimulation periods, akin to a conventional boxcar, Fig. 1A&B, blue, *ii) stimulus period modulation*, since high mu PSP results in a more positive primary BOLD response [2], single-trial mu PSP was assigned to each stimulation period (0-10s) to index the primary response modulation, Fig. 1A&B, red and black, *iii) post-stimulus period modulation*, since high mu PSP leads to a greater BOLD undershoot [2], inverted single-trial mu PSP values were assigned between 10-20s to index post-stimulus modulations, Fig. 1A&B, grey and pink. (IV) Each of the model components was convolved with a single gamma variate function, using a 6 s delay for the driven component and a variable delay of 6-12s for the modulatory components (ii&iii), to best fit to the group HRs.

B) GLM analysis: This optimised three-component model was then used in a GLM analysis for each subject, using individual trial mu PSP to modulate components (ii) and (iii). A fixed-effects analysis was then performed to calculate areas of significant positive/negative BOLD signal correlation with all three model components as regressors across the group (P<0.05, FWE corrected)

Results: The previously published positive (Fig 1E) and negative (Fig 1F) group HRs [2] for upper (red dash line) and lower (black dashed line) mu PSP quartiles can be explained by the three component model shown in Figure 1. The best-fitting gamma variate peak delays were found to be 10s for the modulatory components (ii) and (iii), which led to an excellent fit to the group mean HRs for the upper (red) and lower (black) mu PSP quartiles in both positive (Fig 1E) and negative (Fig 1F) BOLD response regions. Figure 2 shows the results of the group GLM analysis. Figure 2A shows the positive (red) and negative (blue) correlations with component (i) as a regressor, and shows the expected contralateral/ipsilateral S1/M1 response respectively. Figures 2B&C show areas of positive correlation with modulatory components (ii) and (iii) as regressors. We observe that mu PSP modulations index the variability during the stimulus period (Fig 2B) in the sensorimotor, dorsal attention (DAN) and default mode (DMN) networks. In contrast, signal modulations post-stimulation were confined to the sensorimotor network (Fig 2C). No areas showing significant negative correlation between BOLD data and either modulatory component were found.

Discussion: Here, a three component model is formed (Fig. 1) allowing the study of post-stimulus modulations independently from modulations of the primary BOLD response. We identify natural trial-by-trial fluctuations (indexed by mu PSP) during stimulation occurring alongside the constant magnitude of the driven, positive/negative BOLD responses. The modulatory components were found to require convolution with a gamma variate HRF with a longer peak delay (10s) than is conventionally used for the driven response (6s), which is possibly due to different neurovascular coupling mechanisms between the neuronal populations responsible for the different aspects of the response. Here we expand on our original observation that BOLD response modulations both during and post stimulation are indexed by mu PSP [2], to demonstrate that during stimulation these modulations occur over a number of ICNs, whilst the post-stimulus modulations are specific to the sensorimotor network. A high degree of spatial overlap is seen between the map shown in Fig 2B and the DMN, DAN and S1/M1 ICNs (Fig 2D); fusion of these ICNs explains the activity in the cingulate (Fig 2B). We hypothesize that during stimulation these large scale network modulations are related to subjects' attention and cognitive engagement (Fig 2B), whereas the post-stimulus modulations represent bilateral re-setting of the sensorimotor network following stimulus cessation (Fig. 2C), providing a mechanism by which this ICN can return to resting state activity from the lateralised activity driven by stimulation (Fig 2A).

References [1] Shmuel *et al* Nat Neurosci. **9**;2006 **[2]** Mullinger *et al* Proc ISMRM**, 724**;2012 **[3]** Smith et al, PNAS, **106**;2009 **[4]** Wesolowski *et al.* Proc. ISMRM, **6132**;2009 **[5]** Brookes *et al* NeuroImage **40**;2008