Linearity of neural responses in the somatosensory cortex and their relationship to BOLD fMRI.

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Introduction: The relationship between stimulus driven neural activity (measured using EEG/MEG) and the BOLD response (measured using fMRI) has undergone much investigation in order to determine the basis of well characterized non-linearities in BOLD. Both nonlinear neural responses to stimuli and nonlinear vascular responses to neural activity may contribute to BOLD non-linearity and the relative contribution of these two effects remains poorly understood. Recent work[1] has reported that in the visual cortex, non-linear phase locked evoked neural activity only exists at an Inter-Stimulus Intervals (ISI) of less than 200ms[1]. Here we extend this work by investigating the linearity of both the phase locked evoked response, and time locked stimulus driven modulation of oscillatory activity[2] in the somatosensory cortex. Whilst the evoked response lasts only ~100ms, the characteristic stimulus driven loss in β (13-30Hz) band power and the subsequent post stimulus rebound are known to last for up to 2s following stimulus cessation. Given the longevity of this induced power modulation, non-linearities in this response may be evident even at relatively long ISIs. We characterize these neural non-linearities, and we investigate their implications for BOLD studies.

Methods: 8 subjects took part in 2 experiments involving non-painful median nerve stimulation. Electrodes were placed on the subject's right wrist and a 0.5ms voltage pulse was applied causing stimulation of the median nerve and flexion of the middle finger. In the first experiment, 2 pulses were applied with interpulse intervals of 0.25s, 0.5s, 0.75s, 1s, 1.5s and 2s. In the second experiment, trains of 10 pulses were employed with stimulating frequencies of 2Hz and 0.5Hz. In both experiments trials were 8s long and there were 50 trials per condition.

MEG data were recorded for both experiments using the third order gradiometer configuration of a 275 channel CTF system, with a sample rate of 600Hz. Coregistration of MEG data to anatomical MRI was achieved using a head digitization technique (Polhemus Isotrak). BOLD fMRI data were acquired for the second experiment only. In fMRI the 10 pulses were followed by an extended period of rest to allow the haemodynamic response to return to baseline. 20 trials were acquired and the total trial length was 44s. Echo Planar Images were acquired using a Philips 7T MR Archive System (TR=2200ms; TE=26ms; 2mm^3 voxels; 192mm FOV). 21 contiguous transverse slices were acquired covering the sensorimotor cortex.

MEG data were analyzed using Synthetic Aperture Magnetometry[3]. Spatial localisation of power change in the β-band was achieved by comparison of an active contrast window (0-0.5s following stimulation) to a passive contrast window (0.5s of data acquired during the rest period). Pseudo-T-stat images (1mm^3 resolution) were created showing spatially the regions of β-band power change. Estimated timecourses showing electrical activity at locations identified by peaks in the Pseudo-T-stat images were computed using a time domain beamformer technique. The phase locked evoked response was computed by filtering data 1-150Hz and averaging estimated timecourses across trials. For experiment 1, the amplitude of the N20 was computed for the first and second median nerve pulses and their respective ratios calculated and plotted as a function of ISI. The timecourse of β band power change was also obtained (by computing the envelope of oscillatory power fluctuations using a Hilbert transform and averaging envelopes across trials) and the ratio of the integrals of the β-band envelopes for the first and second pulses plotted as a function of ISI. fMRI data were motion corrected and smoothed using a 5mm Gaussian kernel in SPM5. A GLM was employed to identify areas of significant (p=0.05 corrected) BOLD contrast. BOLD timecourses were extracted from volumes of 3x3x3 voxels centered on maxima in the SPM in contralateral S1.

Results: Figure 1 shows the spatial distribution of event-related power loss in β-band activity and significant BOLD signals. The striking colocalisation of these two disparate phenomena strongly suggests that they are linked intimately. Figure 2 [A-F] depicts the changes in β-band power for various ISI's from experiment 1. On the application of a second stimulus during β power loss (within the first 0.5s), the level of desynchronization is maintained. A second stimulus applied during the rebound phase results in immediate desynchronization to the same amplitude as the first decrease. When pulses are 2s apart, two separate rebounds are observed. The duration of modulation in β-band power (up to 2s following stimulation) means that the neural response to subsequent stimulation received during this period may be affected. Fig 3A shows the ratio of evoked response peak amplitude between first and second stimulus. When the second stimulus is applied before the β rebound, the amplitude is smaller than the first. With increasing ISI, ratios increase and when applied near the end of rebound, the ratio approaches 1. Fig3B shows the ratio of the integral of power change between the 2 pulses. With increasing ISI, the ratio decreases to 1. Fig4 shows the BOLD [A] and β band [B] timecourses for experiment 2. Note that the ERS shows an accumulation at the end of the 2Hz stimulation.

Discussion: We have shown that, in somatosensory cortex, modulation in beta-oscillations are prolonged, lasting up to 2s following stimulus cessation. The magnitude of the β-band power loss is always equivalent, irrespective of the starting point, which suggests a gating role for the β response. However, the post stimulus rebound reflects the total number of stimuli presented within a recent timeframe, on the order of several seconds. The N20 peak amplitudes show non-linearities with ISI's of less than 2s, suggesting that the level of beta power at the time of stimulation impacts on the amplitude of the evoked response. These non-linearities in neural activity must be taken in to account when describing the BOLD response and in this case cannot simply be summed linearly according to the number of stimuli. This result is confirmed in experiment 2. The good spatial correspondence of β band activity and BOLD suggests that the two effects are related. However, due to the non-linearities in the underlying neural activity, the BOLD timecourses cannot be explained using simple convolution of either the stimulus or the evoked responses.

Conclusion: We have shown that neural activity exhibits a significantly non-linear response to stimulation, implying that BOLD non-linearity comes not only from a nonlinear vascular response to neural activy, but also a non-linear neural response to the stimulus. This is the case even when the ISI between stimuli is relatively long (on the order of 2s) and the evoked response has returned to baseline.

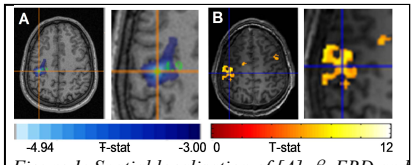

Figure 1: Spatial localisation of [A] β-ERD and [B] significant (p<0.05 corrected) BOLD activity elicited by median nerve stimulation

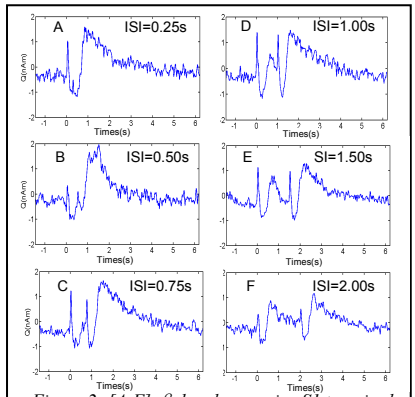

Figure 2: [A-F] β-band power in cS1 to paired pulses with varying ISI.

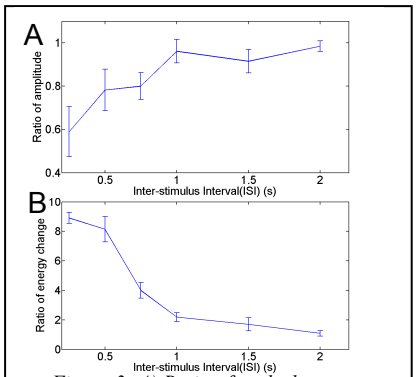

Figure 3: A) Ratio of evoked response amplitude. B) Integrated envelope ratio

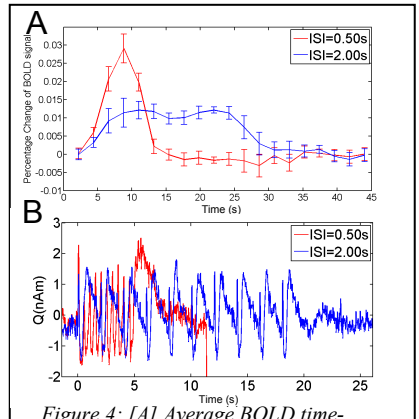

Figure 4: [A] Average BOLD time-courses shown with standard error and [B] β-band oscillations in cS1 from a train of stimuli at intervals of 0.5s (red) and 2s (blue).

References: [1] Z. Liu et al., Proc ISMRM 2009. [2] Pfurtscheller et al., Neuroscience Letters 323 p113-116 (2002) [3]Robinson S, and Vrba J Recent Advances in Biomagnetism, Tohoku Univ Press, Sendai, Japan p302-305,(1998)

Acknowledgements: We acknowledge the Medical Research Council for programme grant support. We acknowledge support from the Engineering and Physical Sciences Research Council, the Wellcome Trust and the University of Nottingham. We also acknowledge the China Research Scholarship.