Assessment of BOLD signal adaptation using single event fMRI at 7 T and its correlation with MEG

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Introduction: Recent studies [1,2] have shown that when stimuli are repeated a number of times the fMRI BOLD response becomes smaller over time suggesting some degree of adaptation of the response. However, the indirect nature of the BOLD response means that it is unclear whether this adaptation is due to reduced metabolic demand driven by decreased neuronal activity, or reduced vascular responsivity. Magnetoencephalography (MEG) directly measures magnetic fields induced by neuronal currents, and therefore offers a more direct measure of neuronal adaptation. The increased contrast-to-noise and signal-to-noise of fMRI at ultra-high field (7 T) allows accurate characterization of single trial haemodynamic responses and the degree of adaptation of the BOLD response can therefore be measured on a trial-by-trial basis. Single trial responses are difficult to record in MEG due to its inherently low SNR, however if a stimulus is repeated a number of times in a single trial, the inter-trial responses can be averaged to obtain an effective single trial evoked response (ER). In the present work we compare the degree of adaptation to a median nerve stimulus measured using both MEG and fMRI at 7 T.

Methods: Data were collected on 3 subjects (age 25 ± 3 (mean ± stdev)) to study the response to repeated median nerve stimulation. 2 Hz non-painful median nerve stimulation (MNS) consisting of a 0.5 ms square wave pulse was performed using surface electrodes placed on the subject's right wrist to cause contraction of the middle finger. The ISI was 18 s and comprised a block (9 s) of repeated stimuli (18 pulses) followed by a 9 s OFF period, repeated for 24 trials.

***fMRI Data Acquisition and Analysis*:** Scanning was carried out on a 7 T Philips Achieva system using a 16-channel SENSE coil. Initially a functional localizer (GE-EPI, TE 25 ms, TR = 1000 s, 20 slices, EPI factor 45, 1.79x1.79x3 mm^3 with 0.5 mm slice gap) was acquired. The study was then performed using 5 slice GE-EPI data acquisition with the same spatial resolution as the localizer but with a TR of 300 ms for optimal sampling of the haemodynamic response. Data were corrected for slice timing, realigned, and temporally smoothed in SPM2. A general linear model was formed with motion parameters as covariates of no interest. Data were modeled as 18 events and a parametric modulation with time used to identify areas displaying adaptation. Time courses of activated areas (using a 3 mm radius sphere) were then extracted. All trials were averaged, and a gamma variate function (variables: amplitude, baseline, onset time and width) convolved with the 18 stimulus events was fitted to the average data to form a haemodynamic response template (Figure 2 (A). A scaling on the amplitude of this template HR was then fitted on a trial-by-trial basis and the resulting fitted percentage change was plotted against trial number and a linear regression performed.

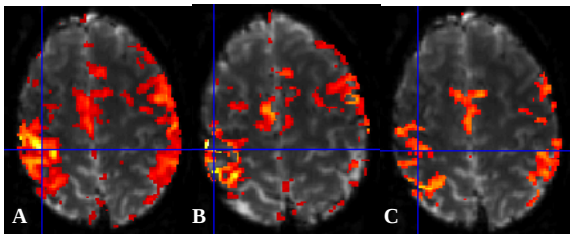

Figure 1: BOLD maps for A) stimulus on, B) areas showing no stimulus adaptation C) areas showing stimulus adaptation (P<0.01)

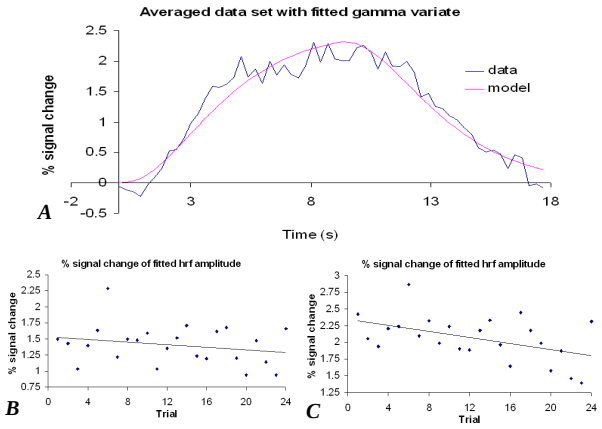

Figure 2: (A) Average HRF across trials and fitted HR template. Fitted BOLD amplitude plotted as a function of trial number for (B) no significant adaptation (gradient = -0.010 +/- 0.009) and (C) significant adaptation (gradient = -0.023 +/- 0.009) .

***MEG Data Acquisition and Analysis*:** MEG data were recorded using the third order gradiometer configuration of a 275 channel CTF whole head MEG scanner (sample rate 600Hz). Source localisation was performed using Synthetic Aperture Magnetometry (SAM). Data were frequency filtered in the 1-40 Hz frequency band. Contrast windows were selected with an 'active' period spanning 100 ms immediately following stimulus onset and a 'passive' period spanning a 100 ms period preceding stimulus onset. Pseudo-T-statistical images showing the spatial distribution of power change between active and passive windows were formed and overlaid onto an anatomical image. Timecourse analysis also used SAM. A location of interest was derived from the peak in the Pseudo-T-statistical image. A 'virtual sensor estimate' was then made to give the timecourse of electrical activity at that location. To assess intra-trial adaptation in the evoked response the timecourse was averaged across the 24 trials; to estimate inter-trial variability the 18 responses in each trial were averaged to obtain a single averaged evoked response per trial. As for fMRI data were fitted to a linear function, and the intra-trial data were fitted to an exponential decay [3].

Results: Figure 1A shows spatial localization of the BOLD response to median nerve stimulation. Figures 1B shows areas that do not exhibit stimulus adaptation whereas figure 1C shows areas that do exhibit stimulus adaptation. These areas are clustered and spatially separate. Figure 2 shows the fitted BOLD amplitude plotted as a function of trial number for B) no significant adaptation and C) significant adaptation. Figure 3 shows the results of the MEG study. Figure 3A shows the spatial location of the evoked response; Figure 3B shows the adaptation of the evoked response within a single trial and figure 3C shows the level of adaptation across all 24 trials. The evoked response shows a definite peristimulus reduction and when fitted to an exponential function adaptation time constants ranged between 6.5 and 24.8s. The adaptation effect across 25 trials showed no significant reduction when fitted to a linear decay.

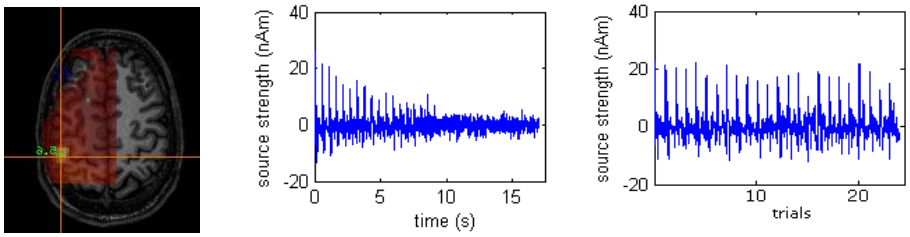

Figure 3: MEG results. A) spatial localization of the evoked response. B) Intra trial average showing adaptation of the evoked response within a single trial. C) Inter trial average showing the level of adaptation of the evoked response on a trial by trial basis.

Discussion and Conclusion: 7T fMRI can be used to measure and fit the haemodynamic response on a trial-by-trial basis in order to characterise the degree of BOLD adaptation across trials. These observations have been compared to adaptation of the evoked response measured using MEG. The BOLD results demonstrate that the response can be split into distinct regions, some exhibiting adaptation and some not. The electrical signal extracted from the peak of the evoked response does not show any inter-trial adaptation, although habituation of the response within a single trial is apparent. This study has found no evidence that the apparent adaptation observed in fMRI is due to decreased neuronal activity related to the evoked response. Further work is in progress to study other features of the MEG response.

References [1] Heckman et al., Neuroimage, 34, 651-660, 2007. [2] Lin, J Neuroscience, 27, 11453-4, 2007 [3] Lammertmann and Lütkenhöner, Clinical Neurophysiology, 112, 499-513, 2001.