# Exploring the relationship between driven neuronal activity and the BOLD response to visual stimulation relative to an individual's alpha frequency.

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## Introduction

Simultaneous EEG-fMRI can be used to explore the correlation of electrical activity and the BOLD response in the human brain. Here we use combined EEG/fMRI to monitor the evoked electrical response and the BOLD response to visual stimuli of varying frequency, where the frequencies are set according to the Individual's Alpha Frequency (IAF). For the purpose of this study the IAF has been defined as the peak measured in the 8-12Hz frequency band from occipital electrodes with the eyes closed. Our aim was to investigate whether the BOLD and driven electrical responses show similar dependence on the frequency of visual stimulation and whether the behaviour is best characterised in terms of absolute frequency or frequency scaled with respect to the IAF.

## Methods

fMRI and EEG data were acquired simultaneously using a Philips Achieva 3.0 T MR scanner and a BrainAmp MR-plus EEG amplifier, Brain Vision Recorder software (Brain Products) and the BrainCap MR electrode cap with 32 electrodes (5kHz sampling rate). A standard EPI sequence was implemented (64×64×20 matrix, 3.25×3.25×3.00 $mm^3$ voxels) with TR/TE =2.2s/40ms and 20 slices were acquired. Cardiac cycle timing was simultaneously recorded using the scanner's physiological monitoring system [1]. The scanner and EEG clocks were also synchronised [2-3]. A Polhemus (Isotrack) system was subsequently used to determine the electrode positions on the scalp. 20 subjects were screened to ensure that they exhibited easily recordable alpha power, and 11 of these subjects were used for the full study. On the day of the full experiment the screening procedure was carried out again to determine the precise IAF of the subject for that day (as slight variations in IAF have been found over time). Stimuli were presented using red LED goggles at (0.6, 0.8, 0.9, 1, 1.1, 1.2, 1.4) ×IAF (these factors were termed 'IAF scaling factors'). These stimuli were presented pseudo-randomly across trials, with a total of 5 trials per frequency and 8s on/20s off for each cycle. 470 EPI volumes were acquired.

## Analysis

_EEG:_ Average artefact subtraction was applied as implemented in Brain Vision Analyzer [4]. Pulse artefact correction was based on R-peak markers derived from the VCG trace [3]. After artefact correction, data were down-sampled to 600Hz sampling rate. A regularised beamformer [5] was then applied to the data recorded with a stimulation frequency of 0.6 x IAF to create a T-stat image showing the spatial variation of driven activation at (0.6×IAF)±2 Hz. This frequency was chosen so as to produce a map least affected by alpha desynchronisation. A timecourse of the electrical response from a virtual electrode placed at the site of peak activity in this T-map was then found for each different driving frequency. The Fourier transforms of the timecourses recorded at each IAF scaling factor were calculated and the power at the driving frequency±0.1 Hz was evaluated.

_fMRI:_ Image processing (realignment, and spatial smoothing with a 3 mm FWHM Gaussian kernel) was carried out using SPM5. fMRI models were set up for all trials within the study, with correction for global effects via standard filtering. The results of this analysis thresholded at p<0.001 (corrected) were used to identify regions of interest (ROI) in the visual cortex. Using the defined ROI, the haemodynamic responses corresponding to each scaling factor were averaged together to form an average response for each frequency of stimulation. The BOLD response was taken to be the percentage difference between the average signal at the HRF maximum±1.5s and at baseline (last 5s of data in each cycle).

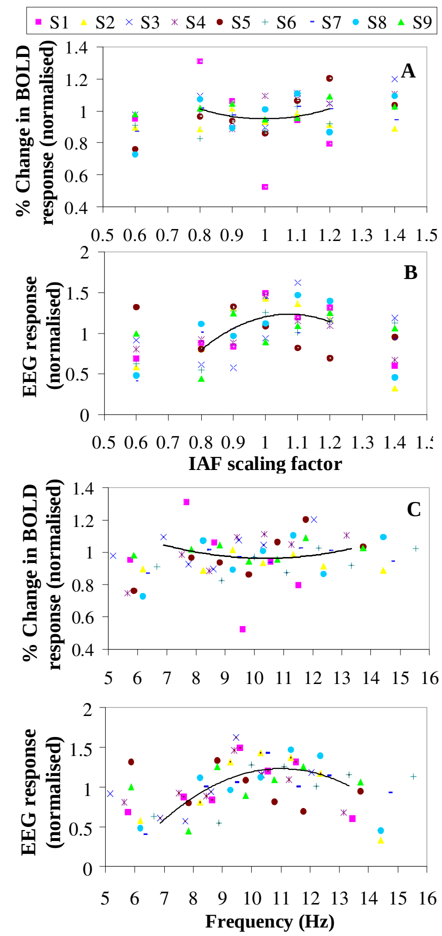


**Figure 1**:*The normalised BOLD* ***(A&C)*** *& EEG* ***(B&D)*** *driven responses plotted against IAF scaling factor* ***(A&B)*** *or frequency* ***(C&D)****. Quadratic lines of best fit show general trends.*

## Results and Discussion

Two subjects were removed from the analysis (due to excessive movement or falling asleep). Figure 1 shows the variation of the strength of both the BOLD and driven responses with the frequency of stimulation. Here, the amplitude of each response has been normalised to the mean response amplitude over all frequencies, for each subject. In Figs. 1A&B the responses are plotted against IAF scaling factor and the lines of best fit are quadratic curves fitted to the five central frequencies (closest to the IAF). It is evident from the data that while the BOLD response appears to decrease slightly when the stimulus frequency is close to the IAF (Fig 1A), the associated power of the EEG response increases more significantly around the IAF (Fig 1B). ANOVA statistical tests were performed on each curve to test for significance of the variation in EEG or BOLD with IAF scaling factor and using the central five frequencies gave p=0.007 and p=0.134 for the EEG and BOLD responses, respectively. Figures 1C&1D show the same data, but plotted against absolute frequency. Quadratic lines of best fit based on the data points lying in the 8-12 Hz frequency band are shown. Performing the ANOVA test on the lines of best fit for this frequency band gave p=0.055 and p=0.125 for EEG and BOLD data, respectively.

The results therefore indicate that the driven electrical responses are best characterised using frequencies scaled relative to the individual's alpha frequency and that the electrical response peaks at stimulus frequencies in the range of 1 to 1.1 x IAF. This is in agreement with the findings of previous studies based on standard EEG measurements [6-7]. In contrast, the BOLD data show less variation with frequency and although there is some evidence for a small dip in the haemodynamic response close to the IAF this did not reach significance. The variation of the BOLD response close to the IAF has not been investigated in detail previously: most fMRI studies have focused on measuring the variation of responses to frequencies spanning a larger range [8-9] and thus have used larger increments in the frequency of stimulation. There is some previous evidence that the frequency of stimulation that generates maximum BOLD response varies across subjects [10], but in our data the BOLD response was not better characterised by plotting against frequency scaled to IAF rather than absolute frequency. Our findings are in agreement with those of a similar study wherein near infra red spectroscopy (NIRS) was used to monitor the haemodynamic response simultaneously with EEG measurements during visual stimulation [7], which showed a peaking of the evoked electrical response close to the alpha frequency which was not accompanied by a significant change in haemodynamic response. These data suggest that the increased evoked electrical activity for stimulation close to the IAF does not cause a concomitant increase in energy demand leading to an elevated BOLD response. The simultaneous recording of the EEG and fMRI data undertaken here ensures that this effect can not be explained by different responses occurring to the stimulus in different experimental environments or by an order effect. The lack of increase in BOLD signal around the IAF may indicate that an increase in the driven response at the IAF reflects phase synchronisation of ongoing background alpha activity rather than the addition of induced neural activity that is unrelated to background activity.

**References [1]** Chia *et al*. JMRI, **12**: 2000. **[2]** Mandelkow *et al.* Neuroimage, **32**(3): 2006 **[3]** Mullinger *et al* JMRI **27**:607-616,2008**[4]** Allen *et al* Neuroimage **8**:229-239,1998 **[5]** Veen *et al*, IEEE Trans. on Biomedical Engineering **44**(9), 1997. **[6]** Pigeau *et al* EEG and Clin. Neurophys. **84**:101-109, 1992 **[7]** Koch *et al* J.of Neuroscience **26**:4940-4948, 2006 **[8]** Ozus *et al* MRI, **19**:21-25, 2001 **[9]**Thomas *et al* MRM, **40**:203-209, 1998 **[10]** Hagenbeek *et al* HBM, **17**:244-250,2002.