Is the habituation of the visual evoked EEG response reflected in the simultaneously acquired BOLD and ASL fMRI signals?

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Simultaneous acquisition of EEG with fMRI is important for defining the extent to which differences in the fMRI response between conditions (e.g. with or without drug), result from actual differences in neuronal activity or differences that could be vascular in origin. EEG-fMRI provides a direct, single-trial means of assessing the coupling relationship between the vascular response and the underlying neuronal activity. In humans, correlations between the amplitude of simultaneously acquired EEG and BOLD measurements of visual-evoked potentials (VEPs) have recently been shown [**1**], but to-date the equivalent EEG-ASL study has not been performed. In this study we investigated the habituation of visual-evoked responses, since there is evidence that both the VEP amplitude and haemodynamic parameters measured by NIRS, decrease during a stimulation period [**2**]. Specifically, we investigated the neurovascular coupling between N75-P100 VEP amplitude and BOLD and GRASE-ASL fMRI responses during simultaneous recordings, with the goal of correlating and BOLD and CBF temporal features with the underlying EEG neuroelectric signals.

Data acquisition: Two experimental sessions of VEP recordings were performed: 1) during continuous BOLD fMRI, 2) during continuous GRASE-ASL measurement at 3T. The stimulus was a 4Hz reversing black and white checkerboard, displayed in the central visual field, in a block paradigm with 30 seconds (120 reversals) followed by 30 seconds of rest. BOLD session: 8 block repeats, ASL session: 16 block repeats. Two cohorts of 11 healthy volunteers were used, aged 25-40, 3 females. Seven of these subjects participated in both sessions.

EEG was recorded with 30 electrodes using an EASYCAP according to the 10-20 system, using a common extra-cephalic reference on the nose. Electrode impedance was kept below 5kΩ. EOG was recorded to remove contaminating eye-blinks using ICA. ECG was recorded to enable subtraction of the ballisto-cardiographic (BCG) pulse artifact. EEG data were digitized at a sampling rate of 2048Hz with an MR-compatible amplifier (Micromed, Treviso, Italy).

Continuous whole-brain T2* weighted, GRE-EPI BOLD images were acquired (TR = 3s, TE = 30 ms, 43 contiguous 3-mm-thick axial slices, image matrix 64 x 64, flip angle 90º) over 184 volumes, corresponding to a total scan time of 9 minutes. Whole-brain GRASE-ASL perfusion-weighted images were collected using a single-shot acquisition at a single inversion time (TI=1200 ms) [**3**]. Low-resolution T_1-weighted anatomical images were acquired with the same orientation as the GRASE-ASL to facilitate registration. ASL images were acquired with the following parameters: TR/TE/TI=3000/39.9/1200 ms, 64 x 64 x 20 matrix, 3.125 x 3.125 x 5 mm^3. Total experiment time 18 minutes.

Data Analysis: EEG data were analysed using EEGLAB (www.sccn.ucsd.edu/eeglab). For both sessions, MRI gradient and BCG pulse artifacts were removed using the FASTR and OBS algorithms [**4**]. Continuous EEG data was down-sampled to 512Hz and band-pass filtered from 0.5-40 Hz and re-referenced to Fz. Single-trial VEPs were extracted using a window from -100 ms pre-stimulus to 250 ms post stimulus. VEPs were averaged across 15 successive trials (VEP_{15}). The grand mean average was also calculated and used in a multiple linear regression fitting [**5**] to measure the N75-P100 amplitude of each VEP_{15}. This generated a time course of 8 (VEP_{15}) amplitude values for each stimulation block. The significance of within-block changes in VEP amplitude was calculated (two tailed t-test).

All fMRI analysis was carried out using FSL 4.0 (www.fmrib.ox.ac.uk/fsl). Sinc-interpolated differencing was used to calculate the GRASE-ASL tag-control subtraction. A double-gamma HRF was used to model the visual cortex haemodynamic response, with post-stimulus undershoot. In addition, a second regressor reflecting a (zero-average) decreasing trend across each stimulation block was incorporated into each subject-level analysis. For both BOLD and CBF datasets, Z-statistic maps of the group response were calculated using a mixed-effects analysis (Z-threshold 2.3). The respective, thresholded group maps were used a functional region of interest (ROI) to extract the mean time-course of BOLD and CBF signal across all subjects. In addition, the significance of the within-block linear trend (second regressor) for both BOLD and CBF, was evaluated by averaging the contrasts of parameter estimates (COPE) within the same ROI, for each subject.

Results: A statistically significant ($p<0.02$) habituation of mean VEP_{15} amplitude during 30-s stimulation blocks was observed in both BOLD and ASL sessions (Fig.1). Robust BOLD and CBF activation to the block stimulus in the visual cortex was measured (max Z: BOLD=5.3; CBF=4.5) (Fig.2) but no significant BOLD or CBF activation was observed in the voxel-wise analysis of the linear trend. However, ROI analysis showed a significant correlation between the decreasing linear trend for the CBF response ($p<0.01$) but not the BOLD response ($p>0.2$). The group mean CBF time-course showed a proportionately larger initial transient increase than observed in the group mean BOLD time-course. This does not translate to a significant difference in CBF between the start and end of the stimulation block (Fig. 3).

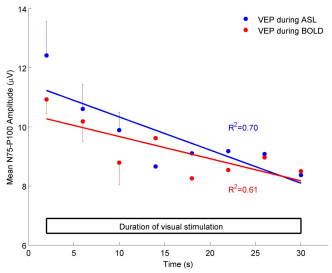

Fig. 1. Group VEP_{15} amplitude during.ASL (blue) and BOLD (red) mean stimulation block. Error bars shown for first three points, standard error in the mean (±SEM).

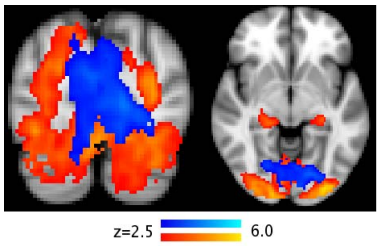

Fig. 2. Group visual-evoked BOLD response (red) and Perfusion response (blue). Coronal y=23. Axial z=33.

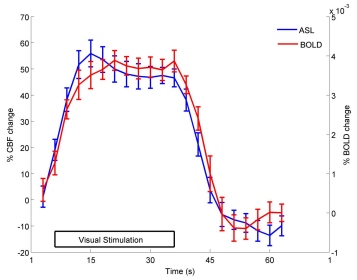

Fig. 3. Group mean time-course of ASL (blue) and BOLD (red) responses to 30s block of visual stimulation. Error bars represent ±SEM.

Discussion: Simultaneous EEG and fMRI enables quantification of the fMRI signal in terms of the underlying neuronal activity, and they permit an interpretation of the neurovascular coupling. The BOLD signal is not a pure measure of cerebral physiology since it reflects the combined effects of changing CBF, CBV and $CMRO_2$, whilst ASL fMRI provides a pure measure of perfusion [**6**]. Our results have shown a significant short-term habituation of N75-P100 VEP amplitude that is not reflected in the BOLD response. However, a subtle decrease in the CBF signal during stimulation blocks has been observed. In support of our findings, evidence exists that the CBF signal may be more localized to the neuronal activity than BOLD fMRI [**7**]; and a previous study reported that the visual-evoked BOLD time-course was not well predicted by EEG responses [**8**]. A close coupling of the vascular BOLD response to the underlying neuronal activity has been previously reported [**9,10**]. However, EEG and fMRI portray different facets of the same neuronal activity and the contribution of mechanisms such as neural inhibition to BOLD is poorly understood. We conclude that the exact characteristics of neurovascular coupling may vary with cognitive and physiological conditions and should be the subject of further investigation

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