Non-linear modulation of both positive and negative fMRI responses to visual stimulation by pre-stimulus occipital EEG alpha power

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Introduction: Recent evidence suggests that brain activity preceding a stimulus, as indexed by the amplitude of oscillatory EEG activity or fMRI signals, can affect the magnitude of the brain's response to that stimulus [1,2,3]. This has important implications for BOLD fMRI measurements of brain activity that are relative to a pre-stimulus "baseline". Occipital EEG alpha power is an electrophysiological marker of subjects' arousal, attention and the excitability of visual cortex [4,5]. Here we use simultaneous EEG-fMRI to investigate the relationship between pre-stimulus alpha power and the magnitude of both positive BOLD (PBR) and negative BOLD (NBR) responses to brief visual stimulation. By explicitly modelling both the continuous alpha power and the interaction between pre-stimulus alpha power and the BOLD response we provide novel evidence that the so-called "baseline" of brain activity can substantially modulate the amplitude of both PBR and NBR to visual stimulation. Our findings have important implications for measurements of brain activation using fMRI, particularly when interpreting how relative BOLD changes relate to the metabolic cost of switching between different states of brain activity.

Methods: *Paradigm:* EEG-fMRI was recorded from fourteen subjects. Three subjects were discarded due to gross movements (>3mm) that resulted in poor quality data. Eleven subjects (4 female, 27.8±5.4 years) remained for further analysis. Individual trials consisted of a single presentation of a left hemi-field black/white checkerboard either high (100%, HC) or low (25%, LC) contrast, phase reversal after 500ms and stimulus-offset at 1s. Subjects fixated throughout on a central fixation cross. 85 trials of each contrast were delivered in total, trials were separated by 16.5–21s. *Imaging:* EEG data were recorded from 64 MR compatible EEG electrodes (Brain Products) during five runs of fMRI using a 3T Philips Achieva scanner. Twenty contiguous gradient-echo axial slices were positioned to cover the occipital cortex (441 volumes/run, 2.5x2.5x3mm voxels, TE = 35ms; TR = 1500ms, SENSE =2, flip angle = 80°). MRI and EEG clocks were synchronised [6].

Analysis: *EEG:* Gradient and pulse artefacts artifacts were corrected using Brain Vision Analyzer [7] and optimal basis sets [8]. Data were concatenated across runs, down-sampled to 500 Hz and filtered into separate VEP (1-25Hz) and alpha (8-13Hz) datasets. *VEPs:* VEPs for HC and LC stimuli were extracted from electrode PO8 (-200ms to +500ms). Single-trial P100-N140 amplitudes were measured [9] and GLM regressors formed from the mean-subtracted parametric modulations in P100-N140 amplitude for each run. *Continuous alpha:* Independent components analysis (ICA) of was used to retain only occipital alpha components in each subject. For occipital channels O1,O2&Oz the mean alpha power (over interval individuals' alpha frequency (IAF) ± 1Hz) during each TR period (0-1500ms) was calculated using FFT. Power was averaged across all 3 channels and mean-subtracted to create a continuous alpha GLM regressor for each run. *Prestimulus alpha:* Alpha data were epoched based on stimulus onsets and for each trial the mean pre-stimulus alpha power (-500ms to 0ms) was calculated using a ±1Hz interval around the IAF. *fMRI:* All fMRI analyses were carried out using FSL 4.1 (www.fmrib.ox.ac.uk/fsl). Data were standardly preprocessed and registered to MNI standard space. Two separate GLM analyses were performed: *VEP-GLM:* Investigated VEP-BOLD correlations using four regressors convolved with a canonical HRF: 1) constant amplitude HC stimulus; 2) constant amplitude LC stimulus; 3) HC VEP; 4) LC VEP. *Alpha-GLM:* To identify brain regions where the amplitude of the BOLD response to the visual stimulus was modulated by the amplitude of pre-stimulus alpha power. The GLM was used to: model the BOLD variance related to fluctuations in continuous alpha power; and model an interaction between the BOLD response and the pre-stimulus (-500ms to 0ms) alpha power, analogous to the psychophysiological interaction method [10]. The multiplication of the constant amplitude stimulus regressor by the pre-stimulus alpha power creates an alpha-interaction regressor. The modulated amplitude of this regressor is non-linearly larger when a stimulus occurs during a state of high alpha power and smaller when a stimulus occurs during low alpha power. First-level GLM analyses used five regressors convolved with a canonical HRF: 1) continuous alpha power; 2) HC stimulus; 3) LC stimulus; 4) PrestimAlpha-HC interaction; 5) PrestimAlpha-LC interaction. A combined contrast of HC+LC>baseline was made for regressors 2-5. Results were combined across all runs with 2nd-level fixed-effects and then across subjects using 3rd-level FLAME1+2 mixed effects ($p<0.05$ cluster corrected). Regions of interest (ROIs) were defined from the conjunction of the interaction with the stimulus PBR and NBR respectively. For each subject, single-trial HC and LC HRFs were extracted (-4.5s to 15s) and converted to percent signal change relative to the first three time-points. For each ROI, separately for each subject, single-trial HRFs were ranked according to the amplitude of pre-stimulus alpha power. Single-trial HRFs were sorted into highest 25% and lowest 25% quartiles according to the amplitude of pre-stimulus alpha power, and averaged across subjects.

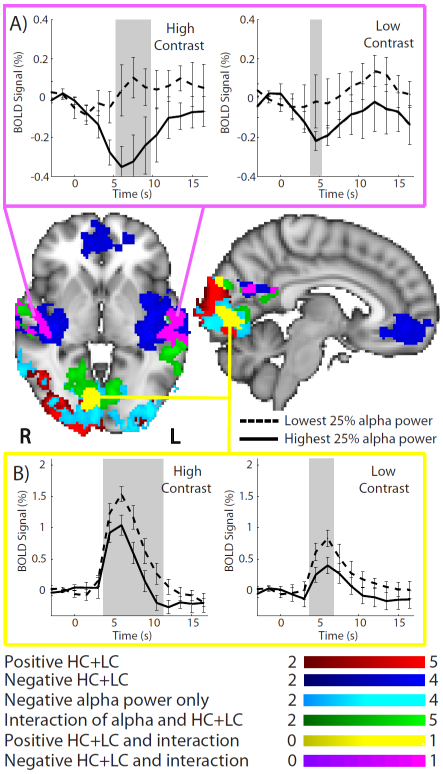

Fig 1. Mixed effects Z-statistic maps of Alpha-GLM results and effect of pre-stimulus alpha power on: NBR HRFs from auditory cortex (A); and PBR HRFs from V1 (B). Grey shading denotes difference between lowest and highest alpha quartiles ($p<0.05$)

Results: *Alpha-GLM:* Left-hemi-field visual stimuli evoked robust PBR in contralateral (right) V1 (Fig 1, red). Significant NBR was observed in bilateral auditory cortex, medial frontal cortex and precuneus (dark blue). The amplitude of continuous alpha power correlated negatively with BOLD in bilateral visual cortex as previously reported (light blue) [11]. Furthermore, a significant *negative* interaction between the amplitude of pre-stimulus alpha power and the amplitude of the BOLD response to the visual stimulus was observed in bilateral primary visual and auditory cortex and precuneus (green). Substantial overlap between the PBR and the alpha-interaction was observed in anterior contralateral V1 (yellow); and between the NBR and the alpha-interaction in bilateral auditory cortex and precuneus (purple). Group mean HRFs extracted from these ROIs show that when a visual stimulus was delivered during low amplitude alpha power, the amplitude of the PBR in anterior contralateral V1 was significantly larger (Fig 1B); and the NBR in auditory cortex and precuneus was significantly smaller (Fig 1A) (i.e. NBR was less negative) than when stimulation occurred during high alpha power. *VEP-GLM:* No significant positive correlation between VEP amplitude and BOLD was observed.

Discussion: We show for the first time that the amplitude of pre-stimulus EEG alpha power significantly modulates the amplitude and shape of both PBR and NBR to a visual stimulus. Contrary to a recent report of a linear effect of alpha upon on the PBR [2], our interaction model suggests both a nonlinear reduction of visual PBR and an enhancement of auditory NBR in trials that are preceded by high alpha power. PBR in contralateral V1 are increased during trials preceded by low alpha power, which we hypothesize reflects greater cortical excitability of V1 [5]. Auditory cortex NBR to a visual stimulus is thought to represent deactivation of non-task relevant processing [12], while increased amplitude of alpha oscillations is understood to represent a mechanism of functional inhibition [4]. This study suggests that the "baseline" state of the brain actually exhibits considerable variability from trial-to-trial which arises from fluctuations in the balance of cortical inhibition/excitation that are represented by increases/decreases in the power of EEG alpha-band oscillations. The consequence of this ongoing electrophysiological variability is modulated amplitude of both PBR and NBR to stimulation. We also found enhancement of NBR responses during high alpha in precuneus areas of the default mode network. Suggesting a functional relationship connecting increases in alpha power, inhibition and NBR where alpha power acts as mediator for inhibition, the strength of which is represented in part by NBR, as a mechanism to improve network processing and responses to the task. Our findings are important for fMRI studies as we show that the amplitude of BOLD responses in primary sensory regions are strongly modulated by the ongoing electrical state of the brain, independent of stimulus properties

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