Trial-by-trial global modulation of BOLD responses to simple, sensory stimuli: implications for functional brain imaging and understanding positive and negative BOLD response coupling

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Introduction: Unilateral stimulation induces contralateral positive (PBR) and ipsilateral negative (NBR) BOLD responses in primary visual (V1), motor (M1) and somatosensory (S1) cortices [1,2,3]. NBR are thought to reflect neuronal inhibition required to optimise task performance by reducing sensitivity to the unattended sensory field [1,2,3], this results in the average magnitudes of PBR and NBR increasing with stimulus intensity [1,3]. However, the functional significance of NBR and their balance with PBR is unstudied at the single-trial level, where signal modulations most behaviourally relevant to the dynamics of network processing are observed [4]. Here we investigate the relationship between natural single-trial variability in PBR and NBR amplitude in V1, M1 and S1 for consistent unilateral stimulation.

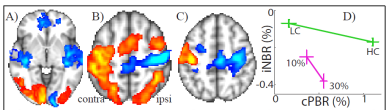

Fig 1. Group average PBR (red) and NBR (blue) to: A) visual (HC&LC), B) motor (10&30%), C) somatosensory stimulation. D) Average PBR and NBR magnitudes for visual (green) and motor (pink) increase with increasing stimulus intensity

Methods: Three experiments were performed in different subject cohorts using a Philips 3T Achieva. Visual. 1s duration left-hemifield checkerboards at either high (100%, HC) or low (25%, LC) contrast were pseudo-randomly delivered to 14 subjects (age=28±5yrs) with inter-stimulus interval (ISI) of 16.5, 19 or 21s, giving a total of 85 trials per contrast/subject. BOLD data acquisition (GE-EPI, 2.5x2.5x3mm^3 voxels, TE=35ms; TR=1500ms, SENSE=2). Motor. 16 right-handed subjects (age=26±4yrs) performed a 5s duration isometric contraction of the right-hand at 10% and 30% of maximum force. 40 trials at each force level were acquired in pseudo-random order, with real-time visual feedback to inform task performance. ISI=5, 7 or 9s. BOLD data acquisition (GE-EPI, 3x3x4mm^3 voxels, TE=35ms; TR=2000ms, SENSE=2). Somatosensory. 10s median nerve stimulation (MNS) was applied to the right wrist (2Hz, 0.5ms pulses at motor-threshold, Digitimer DS7A) of 18 right-handed subjects (age=27±3yrs). Data were recorded over 40 trials with ISI=20s. A FAIR DABS sequence [5] was used to acquire concurrent BOLD and ASL data (background suppression T_{BGS1}/T_{BGS2}=340/560ms; label delay=1400ms; TR=2.6s, TE_{ASL}/TE_{BOLD}=13/33ms, 3x3x5mm^3 voxels, SENSE=2).

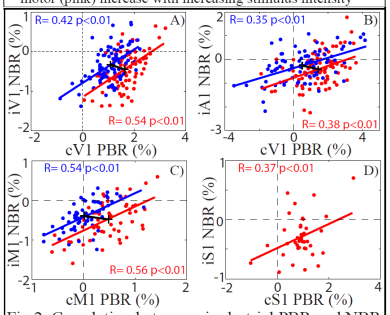

Fig 2. Correlation between single-trial PBR and NBR amplitude in representative subject (median R-value) from A&B) visual, C) motor and D) MNS datasets for low (blue) and high (red) stimulus intensities. Black line indicates negative correlation of mean responses

Analysis: BOLD data were preprocessed using motion correction, 5mm smoothing and high-pass temporal filtering (>0.01Hz). ASL data were used in other analyses [6]. RETROICOR was used to reduce physiological noise in the motor and MNS data. 3/7 subjects were excluded from the Motor/MNS datasets due to excess motion (>3mm). GLM analyses were performed using regressors of stimulus timings convolved with a double-gamma HRF. Group-level activation maps were calculated for positive (PBR) and negative (NBR) stimulus contrasts with mixed effects, p<0.05 cluster corrected (visual and motor) and fixed effects p<0.05 FWE corrected (MNS). Contrasts combining visual HC&LC conditions and 10&30% motor conditions were used to identify common visual and motor response regions respectively. Group-level regions of interest (ROI) were defined by centring a 3x3x3 voxel cube on the peak-statistic BOLD voxel in contralateral (*c*) PBR regions and ipsilateral (*i*) NBR regions of V1, M1, S1 and primary auditory (A1) cortex. Subsequently for each subject and each ROI, single-trial response timecourses were extracted and converted to percent signal change relative to the final three time-points of the mean BOLD response. The mean responses were then used to find the latency of the largest magnitude signal change. Single-trial response amplitudes were measured as the largest peak signal change within the time window: (mean latency±TR*2). For each subject the linear correlation of single-trial PBR-NBR amplitudes was assessed between: *c*V1-*i*V1, *c*V1-*i*A1 for HC and LC visual trials; *c*M1-*i*M1 for 10% and 30% motor trials; *c*S1-*i*S1 for MNS trials. To investigate whether trial-by-trial fluctuations in response amplitude represent a global brain modulation or a confound of changes in respiration, further GLM analyses were performed. Parametric modulations of single-trial PBR amplitude and, where available, the respiratory volume-per-time (RVT) delayed by an 8s lag [7] (motor and MNS) were incorporated as additional regressors, and fixed effects analysis performed (p<0.05 cluster corrected). The modulation due to the RVT was regressed out and single-trial *c*M1-*i*M1 amplitude correlations recalculated for the RVT-corrected data.

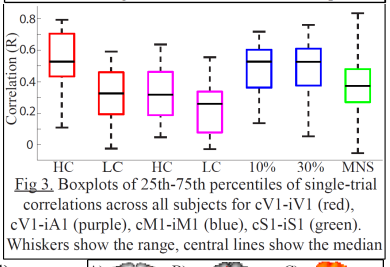

Fig 3. Boxplots of 25th-75th percentiles of single-trial correlations across all subjects for cV1-iV1 (red), cV1-iA1 (purple), cM1-iM1 (blue), cS1-iS1 (green). Whiskers show the range, central lines show the median

Results: Significant contralateral PBR and ipsilateral NBR were observed in V1, M1 and S1 (Fig 1). Additionally, visual stimulation evoked bilateral NBR in A1 (Fig 1A) [8]. In both V1 and M1 the average magnitude of PBR and NBR increased with increasing stimulus intensity (Fig 1D, Fig 2 black lines), in agreement with previous work [1,3]. Trial-by-trial amplitude variability was substantial, mean range across all data: PBR regions -1.1□2.3%; NBR regions: -1.7□1.0%. Bilateral PBR were observed in 24% (visual), 32% (motor) and 14% (MNS) of trials, concurrent with the largest contralateral PBR. We observe a significant (p<0.05) positive, linear correlation between individuals single-trial PBR and NBR amplitudes in visual (HC 12/14 subjects; LC 11/14), motor (10% 11/13; 30% 11/13) and somatosensory cortex (10/11) (Fig 2&3). Visual PBR was also significantly correlated with auditory NBR (HC 11/14; LC 10/14). Figure 3 shows the distribution and median value of the correlation strengths for each condition. No instance of significant negative correlation was observed. GLM analyses showed that single-trial contralateral PBR amplitude was significantly positively correlated with the BOLD response to the stimulus in grey matter across widespread brain regions in all three datasets (Fig 4). The most significant single-trial modulations were observed bilaterally in the directly stimulated primary sensory cortex (Fig 5A). The colour scales in Figure 5 highlight the much greater significance of the single-trial response modulation in bilateral M1 compared to the RVT correlation. Removing RVT modulations from the motor data did not significantly alter the correlation between *c*M1-*i*M1: pre-correction R=0.47±0.19 (Fig 3); post-correction R=0.46±0.22.

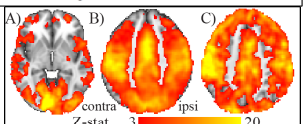

Fig 4. Brain areas correlated with PBR amplitude modulation in cV1 (A), cM1 (B) and cS1 (C) during associated tasks

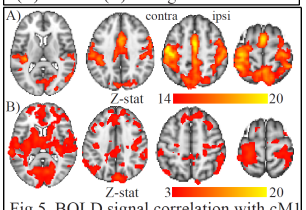

Fig 5. BOLD signal correlation with cM1 PBR (A) and RVT (B) during motor task

Discussion: Using unilateral stimulation in three sensory modalities we demonstrate that the average magnitudes of contralateral PBR and ipsilateral NBR are negatively correlated [1,3] whilst the modulation of single-trial amplitudes are positively correlated. We hypothesize that these contrasting effects arise from two different sources; a response consistently driven by stimulus intensity that is specific to primary sensory cortices, and temporal fluctuations in subject's arousal, attention and spontaneous brain network activity that induce response modulations bilaterally in primary sensory cortex as well as wider brain regions. These widespread single-trial modulations are not detected by conventional, GLM-based functional brain mapping analyses using trial averaging, resulting in a restricted representation of the brain's response to stimulation. The significance and spatial extent of single trial modulation increased with task demand (lowest for brief, passive visual stimulation and strongest for motor, Fig 4). Our paradigms employed different stimulus durations (visual 1s, motor 5s, MNS 10s), ISIs, intensities (visual contrast, motor force) and task-demand (passive for visual and MNS, active response for motor) suggesting that the single trial global modulations are not dependent upon experimental condition and may represent a general response characteristic. By implementing physiological noise and RVT correction we have excluded the possibility that physiological confounds explain the response modulations observed. This combined with the finding that PBR amplitude was independent of both the trial position within the experimental session and pre- and post-stimulus baseline signal in all experiments, suggests that the observed modulations are neuronal in origin. The trial-by-trial correlations we observe reflect global modulation of response amplitude and extend previous findings of widespread activity during visual tasks [9] thus providing a new insight into the complexity of brain responses and the extent of neuronal recruitment by even simple tasks.

References [**1**] Shmuel et al. Neuron 36 2002. [**2**]. Allison et al. Neurology 54 2000. [**3**]. Klingner et al. Neuroimage 53 2010. [**4**] Scheibe et al. J Neurosci 30 2010 [**5**]. Wesolowski et al. ISMRM 6132 2009. [**6**]. Mullinger et al. ISMRM 724 2012. [**7**]. Birn et al. Neuroimage 31 2006. [**8**] Mozolic et al. BMC Neurology 8 2008. [**9**]. Gonzalez-Castillo et al. PNAS 14 2012.