Evoked and induced somatosensory EEG responses predict activity in resting state networks in simultaneous fMRI data during median nerve stimulation.

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Introduction: Use of simultaneous EEG-fMRI is crucial when brain responses to stimulation exhibit unpredictable variations in magnitude, due to factors such as habituation or variation in attention. fMRI studies have shown that brain activity is divided into functional networks of areas whose activity is highly correlated at rest [1]. Recent evidence suggests that the ongoing state of these resting state networks (RSNs) is rich in information and that activity preceding a stimulus can modulate the magnitude of the brain's response to that stimulus [2]. Consequently, the interaction between activity in functionally relevant RSNs and stimulus responses is of great interest. Here we investigate whether RSNs that are known to play a role in task-engagement and attention can be reliably identified from non-resting fMRI data, and ask whether BOLD activity in these areas during median nerve stimulation can be predicted by indices of cortical excitability obtained from EEG stimulus responses.

Methods: Paradigm: 2 Hz median nerve stimulation (MNS) (0.5ms duration pulses, Digitimer DStA) was applied to the right wrist of nine, right-handed subjects to induce motor-threshold thumb movement over 40 block periods (10s on and 20s off, 800 trials total). Imaging: 64-channel EEG (Brain Products system) was recorded both inside and outside the MRI scanner on the same day. fMRI data were acquired simultaneously on a Philips Achieva 3T scanner using a FAIR Double Acquisition Background Suppression (DABS) sequence [3] for concurrent acquisition of ASL and BOLD data (Background suppression at T1/T2=340/560ms; label delay=1400ms; TR=2.6s, T_EA/T_EBOlD =13/33ms, 2x2x3mm voxels, 212mm FOV, SENSE factor 2). Ten contiguous axial slices were aligned in the AC-PC plane to span primary (S1) somatosensory cortex. MRI and EEG clocks were synchronised [4] and cardiac pulse and respiration were recorded. Electrode positions on the scalp were digitised using a Polhemus (Isotrack) system.

Analysis: EEG: Average artefact subtraction for correction of gradient and pulse artefacts was implemented in Brain Vision Analyzer2 [5-6]. Noisy trials and/or channels were rejected. 3 subjects were excluded due to significant (>5mm) motion; one remaining subject exhibited a phase-locked stimulus artefact resulting in poor quality evoked data quality however the mu band activity was unaffected leaving 5/6 subjects for analysis of evoked/induced activity. Data were average-referenced, down-sampled to 600Hz and filtered into two frequency bands: Evoked: 2-4OHz and Mu: 8-13Hz. Virtual Electrode (VE) timecourses were extracted from the location of the peak pseudo t-stat (F) value in contralateral sensory-motor (S1/M1) cortex using a regularised, scalar beamformer [7]. z-stat timecourses of evoked responses were formed using active/passive windows of 0.01-0.16s/0.3-0.45s relative to each individual stimulus whilst mu rhythm z-stat images used active/passive windows of 0.95s/29.5s relative to block onset. VE evoked responses were averaged within stimulus blocks and peak-to-peak P100-N150 somatosensory evoked-potential (SEP) amplitudes measured using an automated linear regression method [8]. The time-course of block SEP amplitudes was mean-subtracted to form a regressor for subsequent fMRI analysis. A continuous block regressor of mu power was formed from the average of the mu rhythm in each active and passive time window.

fMRI: RETROICOR was used to reduce physiological noise in the BOLD data. FLIRT (FSL) was used for motion correction. Further analysis was carried out in SPM8 where BOLD data were normalised to the standard brain and smoothed with a 5mm kernel. GLM analyses: Data were modelled with a boxcar regressor of constant MNS block amplitude and a second regressor of either block BOLD power or block SEP amplitude. Fixed-effects, second level analyses (p<0.001 uncorrected) were performed to investigate areas where the mu fMRI signal was better explained by the EEG parametric modulators than the boxcar. Group ICA: BOLD data were temporally concatenated across all subjects and MELODIC [9] used to decompose the data into 25 maximally independent spatial maps and their associated time-courses. Independent component (IC) spatial maps of recognised RSNs were identified and compared to areas of positive and negative EEG-fMRI correlations. For each area, subjects with a significant positive BOLD correlation with the boxcar (p<0.05 FWE) were used to identify a ROI in contralateral S1. The mean BOLD timecourses (% change relative to the last 3s of the off period) was estimated and averaged across subjects.

Results: Beamformer (BF) source peaks were localised in contralateral S1 for evoked and mu responses outside the scanner in all subjects [10]. Two subjects had no clear peaks in the T-stat images so locations identified outside the scanner were used. Fig. 1 shows data from a representative subject; A) SEP and mu source localisations were highly comparable inside and outside the scanner (mu peaks were within 2.45cm of SEP peak). Fig 1B&C illustrate the high quality of the EEG data; the evoked response and mu desynchronisation measured inside and outside the scanner were highly reproducible inside and outside the scanner. Fig. 2 shows significant positive BOLD responses to the boxcar stimulus, which were observed in contralateral S1, bilateral S2 and supplementary motor area (SMA). Fig 2B shows a robust BOLD response from contralateral S1.

EEG-fMRI correlations: A significant positive correlation between BOLD and SEP amplitude was observed in parietal areas, precuneus and midline frontal gyrus. Significant negative correlations between BOLD and mu power were observed in a bilateral fronto-parietal network comprising of dorsal parietal and lateral prefrontal cortex. Correlations were significant at p<0.05 FWE but for clarity are displayed at p<0.01 uncorrected. IC1: Two ICs corresponding to recognised RSNs were identified for further analysis: 1) default-mode network (DFM) [10]; 2) dorsal attention network (DAN) [11]. Figure 3A illustrates the high spatial overlap of the DFM IC and areas of positive SEP-BOLD correlations (814 voxels overlap, 48% voxels in SEP correlation). Figure 3B shows the overlap of DAN IC and areas of negative-mu-BOLD correlations (1523 voxels overlap, 24% voxels in mu correlation). Although smaller in proportion it should be noted that mu-correlated voxels overlap well with the DAN IC and those voxels which fall outside form part of the same contiguous clusters as those which overlap.

Discussion: Using group ICA of BOLD data we show that synchronous activity within the DFM and DAN networks persists during a MNS paradigm. Further, we find that fluctuations in BOLD signal in the DFM and DAN correlate with evoked SEPs and mu rhythm extracted from simultaneous EEG, suggesting that these reflect functionally relevant variations in subject task engagement and attention. Attention was not explicitly controlled in this study so as to provide natural variability in task responses, as evidenced by EEG-fMRI correlations. It has been widely shown that the DFM is reduced by a consistent amount from its baseline level during a task [10]. We hypothesize that changes in BOLD baseline during the inter-stimulus interval, which reflect the subject’s internal processing, offer an explanation for our results. Subject’s internal mental processing during a simple paradigm such as this may be substantially more cognitively demanding than the task, providing low baseline DFM activity, less awareness of certain stimulus and consequently smaller SEP. Conversely if a subject is more relaxed then a greater awareness of the external stimulus will result in both higher baseline DFM activity and a larger evoked response [12]. Since our SEP modulator does not account for baseline variability, the positive correlation seen is likely to be an artefactual effect of baseline shifts, which cannot be measured from SEP data. The DAN is activated to be directed attention to a task [11]. Our data showed that variations in fMRI activity in DAN are significantly modulated by fluctuations in individual’s continuous mu power; during the task, mu oscillations are suppressed and fMRI activity in the DAN is high. This result is supported by negative BOLD power correlations with alpha power that have been reported as markers of cortical idling during rest [13]. ASL analysis showed a high spatial and temporal correlation with the BOLD boxcar data, and EEG-ASL correlations were in spatial agreement with the RSNs (results not shown). ASL should provide a measure more directly linked to neuronal activity [14]. However, responses were weaker than in the BOLD data due to the lower SNR, and study of an increased number of subjects is needed to allow a fuller interpretation. References [1] De Luca et al. Neuroimage 29(4):1002-1013 (2006); [2] Mandeville et al. Neuroimage 38(3): 2006; [3] Allen et al. Neuroimage 8(3):1998 [6] Allen et al. Neuroimage 12(2):2000. [7] Brooks et al. Neuroimage 45(2): 440-452. [8] Mayhew et al. Clin. Neurophysiol. 117(6):2006. [9] Beckmann & Smith IEEE Trans. Med. Imag. 23(2004). [10] Raiche et al. PNAS 98(2):2001. [11] Corbetta & Shulman Nat. Rev. Neurosci. 3:2002. [12] Schubert et al Cerebral Cortex 18(11):2008. [13] Labus et al Neuroimage 31:2006. [14] Kim et al Neuroimage 21(3):2004.