

Complex and widespread network modulations during simple tasks: trial-by-trial spatio-temporal dynamics of brain function revealed by model-free analysis

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Introduction: Many current implementations of fMRI are limited by analyses that model the response to stimulation as consistent and standardised, ignoring the considerable trial-by-trial variability in response amplitude and morphology [1] that contains the most behaviourally and neurobiologically significant information [2]. Model-free, independent components analysis (ICA) identifies intrinsically-connected networks (ICNs) from coherent patterns of fMRI activity. This enables study of how the interaction of the activities of the brain's functional units gives rise to responses to stimulus inputs. The importance of network dynamics in supporting brain function is becoming increasingly clear [3]. However, the spatio-temporal scales at which ICN dynamics contribute to stimulus responses and task performance remains poorly understood. We address this issue by using ICA to demonstrate the extent to which simple pain and visual stimulation paradigms modulate the trial-by-trial activity of multiple ICNs.

Methods: Two experiments were performed in different subject cohorts using a Philips 3T Achieva. **Pain.** Seventy noxious thermal stimuli (PATHWAY CHEPs, Medoc, Israel, pulse duration = 70ms) were applied to the peroneal area of the right leg in thirteen subjects (age=27±4yrs). Stimulus pulses were delivered at a consistent temperature (53/52/51°C, 2/9/2 subjects) that elicited an average pain rating of 7/10. The inter-stimulus interval (ISI) was 20s. Individual trials consisted of a single stimulation pulse followed by a 10s fixation period before a visual cue instructed the subject to provide a behavioural pain rating using a numerical rating scale. **BOLD data acquisition** (GE-EPI, 3x3x4mm voxels, TE=35ms; TR=2000ms, 32 slices, SENSE=2). **Visual.** 1s duration left-hemifield, black/white checkerboards at 100% contrast were delivered to 14 subjects (age=28±5yrs) with an ISI of either 16.5, 19 or 21s. A total of 85 trials were delivered to each subject. Subjects fixated throughout on a central fixation cross. **BOLD data acquisition** (GE-EPI, 2.5x2.5x3mm³ voxels, TE=35ms; TR=1500ms, 20 slices, SENSE=2).

Analysis: Separately for the pain and visual experiments, BOLD data were motion corrected, spatially smoothed (5mm), registered to the MNI standard brain and temporally concatenated across subjects using FSL 4.1.8 (www.fmrib.ox.ac.uk/fsl). MELODIC was used to decompose the group data into 20 maximally spatially-independent components [4]. Dual regression [5] was used to obtain individual subject timecourses for each component. The component timecourse displaying maximum correlation with the stimulus timings was selected as the primary sensory stimulus-response (visual: contralateral V1; pain: pain network). Four additional bilateral ICNs [6] were selected for further analysis. Visual data: auditory, saliency, default mode (DMN) and dorsal attention (DAN) networks (Fig 1); pain data: sensorimotor (S1/M1), visual, DAN and DMN (Fig 2). For each subject and each ICN, single-trial haemodynamic response (HR) timecourses were extracted and converted to percent signal change relative to the final three time-points of the mean HR. Separately for visual and pain data, the peak latency of the mean stimulus-response HR was found and single-trial amplitudes were measured as the peak signal change within a ±TR time window of this latency. Single-trial HRs of each ICN were then sorted into lower (0-25%), median (37.5-62.5%) and upper (75-100%) quartiles according to the amplitude of the stimulus-response. Repeated measures (RM) ANOVA were then used to test for significant difference in HR amplitude between quartiles.

Results: Model-free analysis revealed that extrinsic stimulation differentially modulates the BOLD signal in a complex manner in regions widely distributed across the brain (Fig 1&2). On average, visual stimulation induced BOLD signal increases in contralateral V1 and DAN with BOLD signal decreases observed in bilateral auditory cortex and the DMN. A biphasic response was observed in the saliency ICN with an initial signal increase followed by a similar magnitude decrease. The pain stimulus-response ICN comprised of thalamus, bilateral insula, bilateral orbitofrontal cortex and anterior cingulate. On average, pain stimulation additionally induced BOLD signal increases in S1/M1 and the DAN with BOLD signal decreases observed in visual cortex and the DMN. Sorting single-trial ICN timecourses by the amplitude of the stimulus-response revealed detailed and widespread brain dynamics both preceding and in response to stimulation (Figs 3&4). Considerable trial-by-trial variability in the stimulus-response amplitude was observed: visual 0.01-4.3%; pain 0.18-1.1%. The upper quartile of primary visual response trials was associated with BOLD signal increases in auditory cortex. Responses in the saliency ICN and DAN displayed a high degree of variability in HR morphology and amplitude between quartiles. Upper quartile trials displayed significantly elevated pre-stimulus BOLD signal in both networks, which respectively developed into a negative BOLD response in the saliency ICN but increased to a positive BOLD response peak followed by an undershoot in the DAN. In contrast, lower quartile saliency trials displayed a BOLD signal increase. No significant difference in DMN amplitude was observed between quartiles. The upper quartile of pain response trials was associated with significantly larger BOLD response amplitude (peaking at ~6s) in all other ICNs, although HR morphology again showed a high degree of variability. The DAN HR was long lasting with a double peak (8 and 18s). The visual cortex BOLD response was negative on average but with a signal increase at 8s. Lower quartile trials displayed significantly elevated pre-stimulus BOLD signal in the DMN that was followed by a strongly negative DMN response. In contrast, a slightly increase in BOLD signal was observed in the upper quartile of DMN trials.

Discussion: Single-trial analyses revealed the inherent complexity contained in the brain responses to simple stimulation paradigms. Widespread brain regions, comprising multiple ICNs, are extensively modulated by brief visual and pain stimulation. This modulation occurs at multiple time-points throughout the trial and results in great diversity in the shape and polarity of the trial-by-trial response. Furthermore, the pre-stimulus BOLD signal amplitude in the DAN and DMN was found to predict the amplitude of the subsequent visual and pain stimulus-responses respectively. This suggests that DAN/DMN activity plays a central role in supporting brain function and can influence the processing of spatially distinct sensory areas, dependent upon task modality. By studying multiple ICNs throughout the whole response timecourse, this study extends previous work demonstrating that ICN activity can contribute to and modulate the behavioural/brain response through: ongoing processes that facilitate short-term, network response priming [7]; active, concurrent signaling during task performance [7]. Our simple trial sorting approach provides insight into the modulation of ICN dynamics that may influence the primary response, regulate attention and support task performance. Studying other response parameters, across multiple ICNs could reveal yet more detailed insight into the complex network dynamics underlying brain responses. Conventional analyses modelling the BOLD response as a consistent, canonical HRF, or using across-trial averaging, utilize only a fraction of the rich information contained in the data. Here, whilst the median and upper quartiles of stimulus-response HRs resemble the canonical HRF, the average HR's of the other ICN's diverge substantially even before trial-by-trial variability in the shape and amplitude of the response is considered. The pre-stimulus modulations observed in the DAN and DMN and the polarity reversals in other ICNs are only evident using single-trial analyses. While the canonical HR has enabled functional localisation studies, it has become an outdated oversimplification, restricting the ability to extract the most meaningful information from the data. Our data suggests that single-trial contributions of brain processes at multiple spatio-temporal scales should be considered to move beyond GLM-based methodologies and towards assembling a better understanding of the parallel complexity of brain function.

References [1] Duann et al Neuroimage 15 2002. [2] Scheibe et al. J Neurosci 2010. [3]. Bressler&Menon, Trends Cogn Sci 14 2010. [4]. Beckmann&Smith IEEE Trans. Med. Imag. 23 2004. [5] Beckmann et al HBM, San Francisco. 2009. [6]. De Luca et al. Neuroimage 29 2006 [7]. Sadaghiani et al J Neurosci 29 2009. [8]. Fox et al Neuron 56, 2007.

