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Intrinsic variability in the human response to pain is assembled from multiple, dynamic brain processes

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ABSTRACT

The stimulus-evoked response is the principle measure used to elucidate the timing and spatial location of human brain activity. Brain and behavioural responses to pain are influenced by multiple intrinsic and extrinsic factors and display considerable, natural trial-by-trial variability. However, because the neuronal sources of this variability are poorly understood the functional information it contains is under-exploited for understanding the relationship between brain function and behaviour. We recorded simultaneous EEG–fMRI during rest and noxious thermal stimulation to characterise the relationship between natural fluctuations in behavioural pain-ratings, the spatiotemporal dynamics of brain network responses and intrinsic connectivity. We demonstrate that fMRI response variability in the pain network is: dependent upon its resting-state functional connectivity; modulated by behaviour; and correlated with EEG evoked-potential amplitude. The pre-stimulus default-mode network (DMN) fMRI signal predicts the subsequent magnitude of pain ratings, evoked-potentials and pain network BOLD responses. Additionally, the power of the ongoing EEG alpha oscillation, an index of cortical excitability, modulates the DMN fMRI response to pain. The complex interaction between alpha-power, DMN activity and both the behavioural report of pain and the brain's response to pain demonstrates the neurobiological significance of trial-by-trial variability. Furthermore, we show that multiple, interconnected factors contribute to both the brain's response to stimulation and the psychophysiological emergence of the subjective experience of pain.

Introduction

In the course of everyday life the human brain is continually bombarded by sensory information and generates a behavioural response proportionate to the varying intensity and saliency of each event. Functional neuroimaging experiments simulate a constrained version of this scenario in a laboratory environment and primarily use the signal change evoked in response to a stimulus event to elucidate the timing, intensity and spatial location of the underlying brain activity. Conventional fMRI and EEG analyses assume that the brain's response is standardised and consistent across repeated stimulus presentations. However, studies ranging from single-neuron recordings to macroscale neuroimaging indicate that not only is response variability intrinsic to brain function but that it contains perceptually relevant information (Debener et al., 2006; Scaglione et al., 2011; Scheibe et al., 2010). The functional and behavioural significance of this variability and the neural substrates underlying it remain poorly understood.

Human pain is a conscious, subjective interpretation of nociceptive input influenced by cognitive, neurophysiological and environmental factors (Legrain et al., 2002; Tracey and Mantyh, 2007). Consequently, both the perceptual and the brain responses evoked by pain exhibit considerable natural variability both between individuals and across multiple experimental trials (Coghill et al., 2003; Nielsen et al., 2009; Stancak et al., 2011). The perception of pain from nociception is generated by a spatially-distributed network of brain regions (Apkarian et al., 2005; Peyron et al., 2000) and recent fMRI studies have highlighted the importance of studying network dynamics for understanding the emergence of pain (Boly et al., 2007; Ploner et al., 2010). Such work reflects a conceptual shift towards an appreciation of the importance of understanding the functional architecture of the brain as represented by intrinsically connected networks (ICNs), whose regional activity is correlated during the resting-state, and modulated by external inputs (Smith et al., 2009). Pain stimulation is therefore an ideal candidate system in which to investigate the ability of multimodal neuroimaging to provide trial-by-trial spatiotemporal dissociation between regional

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brain responses to stimulation, and to probe the contribution of network dynamics to the brain response.

The importance of brain network dynamics in supporting cognitive function is becoming increasingly clear (Bressler and Menon, 2010). We broadly summarise the contribution of ICN dynamics to task performance and behavioural outcomes at three spatio-temporal scales as: 1) (*Ongoing*) facilitating short-term, network response priming such that pre-stimulus ICN activity influences the behavioural and/or brain response to a subsequent stimulus (Becker et al., 2011; Sadaghiani et al., 2009); 2) (*Concurrent*) providing an active contribution through signalling occurring during task performance (Fox et al., 2007; Kelly et al., 2008); 3) (*Intrinsic*) defining core properties of ICNs, such as resting-state signal coherence, that determine parameters of behavioural (Mennes et al., 2011) or brain responses (Kannurpatti et al., 2012; Keller et al., 2011).

Here we use simultaneous EEG–fMRI recordings during rest and fixed-temperature, noxious, thermal stimulation to investigate the contributions of these three mechanisms to the natural variability in behavioural and brain responses. EEG–fMRI presents a powerful tool to study this phenomenon as: 1) fMRI provides the high spatial resolution whole-brain coverage required to measure the activity of the distributed brain areas that comprise ICNs; 2) EEG records the dynamics of brain activity directly, providing measurements of neuronal response features with high temporal resolution. This allows investigation of how variability in these features correlates with regional haemodynamic response amplitudes; 3) Indices of cortical excitability, such as the 8–13 Hz alpha oscillation which has been shown to modulate subsequent behavioural and brain responses (Becker et al., 2011; Hanslmayr et al., 2007; Linkenkaer-Hansen et al., 2004), can be measured from EEG and their effect upon simultaneous fMRI signals observed.

It is important to characterise both inter- and intra-subject response variability in order to fully understand the link between the brain's response to pain and the subjects' perception of pain. However, the majority of neuroimaging studies analyse only a subset of potential functional indices which restricts interpretation of the complex and parallel brain processes underlying a given behaviour. In this study we aim to take a more comprehensive approach, by investigating the influence of multiple ICNs at a range of temporal scales. This demands both a multimodal neuroimaging approach and an integrative analysis framework, combining the dynamics of pre- and peri-stimulus neuroelectric and haemodynamic ICN activity with event-related responses. We utilise three analysis strategies: 1) investigating the Intrinsic mechanism through the relationship between task-evoked fMRI responses in the pain network and the resting-state functional connectivity of this network; 2) studying the Concurrent mechanism by investigating the origins of the natural variability in the brain's response to pain stimulation using GLM analyses featuring single-trial parametric modulations of either pain-ratings or EEG evoked potential amplitudes. Additionally, the modulation of the fMRI response to pain by Ongoing cortical excitability is tested by integrating spontaneous EEG alpha-power with stimulus timings in the GLM; 3) using model-free independent components analysis to identify ICNs additional to the pain network and investigating how their fMRI signal modulations vary with the pain fMRI response, the EEG response and the behavioural response. Studying pre- and post-stimulus fMRI signals in these ICNs provide a method to identify the influence of Ongoing and Concurrent mechanisms respectively. Using these methods we demonstrate for the first time that multiple, spatio-temporal brain processes contribute to the subjective experience of pain.

Materials and methods

Experimental paradigm

Simultaneous EEG–fMRI data were recorded in 16 subjects (8 female, mean age ± SD 24.3 ± 3.8 years). Written informed consent was obtained from all participants and the protocol was approved by the Research Ethics Board of the University of Birmingham. Thermal pain stimuli were applied to the perineal area of the right leg at two temperature conditions (PATHWAY CHEPs, Medoc, Israel). Rapidly delivered, noxious contact heat stimulation activates both Aδ- and C-fibre mechano-heat skin nociceptors leading to robust and reproducible fMRI responses in the pain network (Roberts et al., 2008) and well characterised contact heat evoked potentials (CHEPs, (Chen et al., 2001; Warbrick et al., 2009)). During a preliminary testing session, immediately prior to scanning, the high condition was selected as the stimulus temperature that elicited an average subjective pain report of 7/10 on a numerical rating scale (NRS), high temperature was 53 °C (3 subjects); 52 °C (10 subjects); or 51 °C (3 subjects). The low temperature condition was always set 2 °C below the high, and elicited an average subjective pain report of 4/10. During a twelve-minute experimental run, thirty-six stimuli of one temperature condition were delivered separated by an inter-stimulus interval of 20s. Two experimental runs were acquired for each temperature, resulting in seventy-two trials per condition. Run order was counterbalanced across subjects. Individual trials consisted of a single thermal pain stimulus followed by 12 s of central fixation before a visual cue (6 s central display of the word "Rate") instructing the subject to report a behavioural pain rating using a 0–4 NRS (0 = no pain and 4 = severe pain). Between stimuli the baseline temperature of the thermal probe was maintained at 32 °C. Stimuli were delivered to exactly the same area of the leg for two consecutive stimuli and then the probe was moved to an adjacent area to prevent sensitisation to the stimulus. Within the same session, following the first two stimulus runs, a six-minute resting-state scan was also acquired, during which subjects were instructed to lie still, keep their eyes open and think of nothing in particular.

Data acquisition

All experiments were conducted at the Birmingham University Imaging Centre (BUIC) using a 3 T Philips Achieva MRI scanner. An eight channel phased-array head coil was used to acquire T1-weighted anatomical image (1 mm isotropic voxels) and whole-brain T2*-weighted, functional EPI data (3 × 3 × 4 mm voxels, TR = 2000 ms, TE = 35 ms, SENSE factor = 2, flip angle = 80°). Cardiac and respiratory cycles were continuously recorded (pulse oximeter and respiratory belt). EEG data were recorded from 62 scalp Ag/AgCl ring-type electrodes distributed according to the 10–20 system with two additional channels used for recording the ECG and electrooculogram. The impedance at all recording electrodes was maintained below 20 kΩ. A BrainAmp MR-plus EEG amplifier (Brain Products, Munich) was used for recording data at 5 kHz with 0.016–250 Hz hardware filters. Subjects were positioned such that electrodes Fp1 and Fp2 were at the magnet isocentre in the foot/head direction so as to minimise gradient artefact (Mullinger et al., 2011). The EEG clock was synchronised with the MR scanner clock, with the TR equal to a multiple of the EEG sampling period, to ensure consistent sampling of the waveforms (Mullinger et al., 2008).

EEG analysis

EEG data were corrected for MRI gradient and pulse artefacts using average-artefact subtraction in Brain Vision Analyser 2 (BrainProducts, Munich). Data were subsequently down-sampled (500 Hz), filtered (1–30 Hz) and converted to average-reference. For each subject, data were concatenated across all four thermal stimulus runs and processed with independent component analysis (fastICA (Hyvarinen, 1999)). Components with non-physiological power spectra or scalp distribution that represented residual pulse or eye-blink artefacts were removed.