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Dissociating nociceptive modulation by the duration of pain anticipation from unpredictability in the timing of pain

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ABSTRACT

Objective: Waiting longer to receive pain increases its perceived unpleasantness by inducing 'dread'. However, it is not clear how unpredictability in the timing of the impending pain stimulus interacts with dread and whether the two factors show differential effects on the neural generators of the pain-evoked response.

Methods: We manipulated the duration of anticipation of laser-induced pain independently of unpredictability of stimulus delivery timing, to observe the relative effect on P2 amplitudes of the laser-evoked potential (LEP) response and its estimated sources.

Results: Subjects ($n = 12$) reported increased pain ratings after longer pain anticipation, irrespective of unpredictability in the timing of stimulus delivery. By contrast, unpredictability in stimulus timing increased the amplitude of the P2 irrespective of anticipation duration. The modulation of P2 amplitude by unpredictability was localized to midcingulate cortex (MCC) and ipsilateral secondary somatosensory (S2) areas. Greater anticipation duration increased activity in a hippocampal-insula-prefrontal network but not in MCC areas.

Conclusions: Distinct neural networks contribute to the P2 and are differentially affected by pain anticipation duration and unpredictability in stimulus timing.

Significance: ERP research into dread should be careful to appreciate the neural generators of pain-evoked responses and their potential modulation by unpredictability.

1. Introduction

The experience of pain integrates sensory information about the intensity, timing and location of the stimulus with cognitive and affective information (Melzack and Wall, 1965; Craig, 2003). Pain is mediated through a network of distributed areas in the brain, the pain matrix (Melzack, 2001). The pain matrix consists of the medial pain system associated with processing the affective and motivational aspects of pain and the lateral pain system responsible for encoding sensory-discriminative information and motor coordination responses (Jones et al., 2003; Vogt, 2005). Although these two pain systems can be differentiated (Kulkarni et al., 2005; Rainville et al., 1999), it is clear that changes in the sensory characteristics of pain modulate the affective value of the stimulus (Price, 2000).

One way in which the affective characteristics of pain can be modified is by altering the timing of the stimulus. As is common in dealing with unpleasant events, most people would choose to have a painful stimulus delivered quickly rather than wait for it (Berns et al., 2006). This phenomenon extends to choosing to have a *more* painful stimulus given sooner rather than wait for a less painful one (Berns et al., 2006). Behavioral models (Caplin and Leahy, 2001) assume this occurs because there is a cost to waiting, i.e., dread. Using functional magnetic resonance imaging (fMRI), the neural correlates of dread during anticipation of pain have been localized to key areas of the pain matrix including midcingulate cortex, primary and secondary somatosensory cortices, and posterior insula cortex. A further study utilized the temporal resolution of electro-encephalography (EEG) and magneto-encephalography (MEG) to specifically look into the effects of longer anticipation periods on the pain-evoked response (Hauck et al., 2007). It showed that longer pain anticipation durations increase the amplitude of the P2 component, which is known to be generated mainly from the midcingulate cortex (Bentley et al., 2003; Garcia-Larrea et al., 2003), in addition to augmenting pain experience. However, research has also revealed potential sources of the P2 in posterior parietal, medial temporal and anterior insular regions (Bentley et al., 2001; Valeriani et al., 2000). It is not clear which P2-generating brain regions contribute to the

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increased pain unpleasantness resulting from longer pain anticipation durations.

One factor that may interact with the length of anticipation and its associated dread is unpredictability in the timing of the painful event. Predictability in general determines the level of uncertainty with which a pain stimulus is anticipated, and may take the form of uncertainty about the intensity, location, timing or type of a stimulus. Predictability has an adaptive value, in that it allows organisms to develop behavioral control strategies, and like control, predictability can modulate the extent to which aversive stimuli induce stress and anxiety (Miller, 1981).

No study to date has controlled for the possible modulatory influences of unpredictability in stimulus timing when investigating the effects of anticipation duration on pain responses. Attention may be modulated by unpredictability in a way that modifies the pain-evoked response. The importance of attention in modulating the pain response is widely acknowledged (Buffington et al., 2005; Keefe et al., 2004; Bantick et al., 2002; McCaul and Haugtvedt, 1982; Hauck et al., 2007; Kulkarni et al., 2005). Both theoretical considerations and evidence suggests that that any kind of uncertainty (Dayan and Abbott, 2001; Brown et al., 2008), and specifically uncertainty in the timing of pain (Carlsson et al., 2006), modulates attention to the stimulus. Research using fMRI has shown that varying the unpredictability of stimulus timing causes differential brain responses in areas associated with attention and affective processing (Carlsson et al., 2006). Hence it is important to control as far as is practical for the effect of attention in order to accurately ascertain the effects of uncertainty and anticipation period duration on pain responses.

The aim of this study was to investigate the effects of both anticipation duration and unpredictability of stimulus timing on pain-evoked responses and perceived pain, whilst controlling for possible modulatory effects of attention. We manipulated the unpredictability in the timing of pain delivery, independently of the anticipation duration, allowing us to determine the main effects of each. We predicted that increasing the anticipation duration would increase the perceived painfulness of the stimuli, independently of their unpredictability. We expected this effect to be associated with increased pain-evoked responses in areas of medial pain system associated with pain unpleasantness, including midcingulate cortex. We further expected that manipulation of the unpredictability of pain would modulate attention-related activity in midcingulate cortex independently of anticipation duration.

2. Methods

2.1. Subjects

Twelve healthy, right-handed subjects, free of psychiatric, neurological, cardiovascular or autonomic disorders, participated in the study (mean age 21.25 ± 2.0). Subjects gave informed written consent, and the study was approved by Oldham Local Research Ethics Committee.

2.2. Experimental procedure

Laser heat stimuli of 150 ms duration and a beam diameter of 15 mm were applied to the dorsal surface of the subjects' right forearm using a CO_2 laser stimulator. Between stimuli, the laser was moved randomly over an area 3 cm × 5 cm to avoid habituation, sensitization or skin damage. Subjects wore protective laser safety goggles during the experiment.

An initial psychophysics procedure was performed using a 0–10 sensory rating scale, which was anchored such that a level 0 indicated no sensation, level 4 indicated the pain threshold and a level 7 indicated moderately painful. Participants were told to regard 'moderately' painful as halfway between pain threshold and the maximum they could tolerate (which also corresponds to how the level 7 is defined on the scale – halfway between level 4 (threshold) and 10 (tolerance)). A ramping procedure was repeated three times to determine laser intensities rated as a level 7, for each subject. Subjects' ratings of the intensity level were then tested through a series of laser pulses and the intensity levels were adjusted to achieve an appropriate level of sensation.

The start of each trial was indicated by the presentation of a visual stimulus on a computer screen. Participants were made aware that the laser stimulus would be delivered at either 3, 6, 9, or 12 s and that there was an equal probability of any trial occurring. Three seconds was chosen as the minimum anticipation duration to remain consistent with our previous studies (Brown et al., 2008; Brown et al., in press; Brown and Jones, 2008), in which we aimed to separate early and late anticipatory processes. By maintaining this separation for the shortest anticipation periods in the present study we ensured no overlap of early anticipatory processes and those related to pain processing. Multiples of 3 s were used for further conditions so that anticipation duration could be regarded as a linear variable in statistical analyses.

There were two experimental conditions, predictable and unpredictable, that differed according to the subject's knowledge of the timing of the laser stimulus. In both conditions a number was displayed in a blue triangle prior to the stimulus delivery, but only in the predictable condition did the number indicate the timing (in seconds) prior to the stimulus: numbers were displayed within a downwards-pointing triangle, which counted downwards starting at 3, 6, 9, or 12 (representing the number of seconds until stimulus delivery) until the delivery of the laser stimulus at time zero. By contrast, in the unpredictable condition there was no clue as to when the pain stimulus would be given. The unpredictable condition was represented by blue triangles pointing upwards, in which the numbers counted upwards beginning with the number 1, and ending on 3, 6, 9, or 12 depending on the anticipatory period duration. Hence, in both conditions the anticipatory visual stimuli changed once every second until stimulus delivery. Our design therefore prevents attentional lapses that may occur during longer anticipatory periods when there is a relative lack of novel sensory input. We reasoned that such lapses in attention may inadvertently influence pain responses. Such exogenous cues have in the past been used to maintain attention, showing measurable effects on attention areas in the brain (O'Connor et al., 2005).

Following the laser stimulus (given at the pre-determined level 7 in all trials) there was a 3 s resting period, during which time participants were asked to remain still and focus on the screen ahead, awaiting the next prompt. This allowed EEG recording of the LEP. The participant was then prompted to rate the painfulness of the stimulus by the appearance of the 0–10 pain scale on the computer screen. The experimental design is schematically represented in Fig. 1.

Each of the 8 trial conditions (i.e. the 4 anticipation durations (3 s, 6 s, 9 s, and 12 s) ×2 predictability conditions) was presented 20 times across 4 blocks lasting approximately 10 min each. Trials were presented in a pseudo-random order with each block containing 5 of each trial type. This ensured that each condition was evenly distributed through the experiment and prevented habituation interfering with condition effects. Subjects were made aware that the probability of receiving each condition was the same on each trial.

EEG recordings were taken from 61 scalp electrodes placed according to an extended 10–20 system (Easycap coupled with Neuroscan amplifiers). Electrodes were referenced to the ipsilateral (right) earlobe, and recordings were also taken from the contralateral (left) earlobe for off-line conversion to linked ears reference.