# The threat of predictable and unpredictable pain: Differential effects on central nervous system processing?

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Central nervous system performance is disrupted by pain and by the threat of pain. It is not known whether disruption caused by the threat of pain is dependent on the likelihood of pain occurring. We hypothesised that when a painful stimulus is possible but unpredictable central nervous system performance is reduced, but when the pain is predictable and unavoidable it is not. Sixteen healthy subjects performed a reaction time task during predictable and unpredictable conditions (100% and 50% probability of pain, respectively). Group data showed increased reaction time with the threat of pain by 50 ms (95% CI 16 to 83 ms) for the predictable condition and 46 ms (95% CI 12 to 80 ms) for the unpredictable condition ($p < 0.01$ for both), but there was no difference between predictable and unpredictable conditions ($p = 0.41$). However, individual data showed that there was a differential effect in 75% of subjects ($p < 0.05$ for all) and that there was a greater effect of predictable pain for some subjects and a greater effect of unpredictable pain for others. Reaction time was related to reported anxiety ($r = 0.49$, $p = 0.02$ for both conditions). The predictability of a painful stimulus may have a differential effect on central nervous system performance within individuals, but anxiety about the impending pain appears to be important in determining this effect. **[Moseley GL, Brhyn L, Ilowiecki M, Solstad K and Hodges PW (2003): The threat of predictable and unpredictable pain: Differential effects on central nervous system processing? Australian Journal of Physiotherapy 49: 263–267]**

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## Introduction

Pain demands attention and takes priority for central nervous system resources so that stimulus processing and response selection are disrupted. For example, cognitive performance tasks (Crombez et al 1998a, Crombez et al 1999, Eccleston and Crombez 1999), brain imaging studies (Derbyshire et al 1997, Derbyshire et al 1998), recordings of event-related potentials in the cortex (Rosenfeld et al 1993) and a combination of these methods (Lorenz et al 1997, Lorenz and Bromm 1997) indicate longer latencies to cortical and behavioural responses and more errors in performance with pain than without pain. This impact of pain on central nervous system performance has been termed pain interference (Crombez et al 1997).

A common method of investigating pain interference is to use a primary task paradigm in which subjects have to attend away from a painful stimulus in order to effectively perform a cognitive task. Interference is recognised by a reduction in speed and accuracy of task performance (Crombez et al 1994, Eccleston 1994). The data show that pain has a dramatic effect on performance (Crombez et al 1994) and that the effect habituates, which suggests that pain alone is not the sole determinant of the disruption to performance (Crombez et al 1997).

In chronic pain patients, the primary task paradigm has been used to demonstrate that the impact of pain is greatest in those with severe pain and those that are hypervigilant to somatic information (Eccleston 1994, Eccleston 1995). The latter finding suggests that the impact of pain is dependent on its threat value. Not surprisingly then, the mere threat of pain also demands central nervous system resources. In healthy subjects, Crombez et al (1998a) showed increased disruption of task performance with a low-pain stimulus when subjects were told a very painful stimulus would follow. Our group has observed increased reaction time to an arm movement task when subjects are told to expect a painful cutaneous shock even though none is delivered (Moseley 2001). In chronic pain patients, Crombez's group has demonstrated greater impact in those patients who have catastrophic thought processes about their pain than those who do not (Crombez et al 1998b).

One issue that remains unresolved is whether the impact of the threat of pain is affected by the likelihood of its occurrence. Extensive data suggest that endocrine and behavioural stress responses are greater when an impending stressor is uncertain (Abbott et al 1984, Tsuda et al 1989), but there is debate as to whether the difference lies in the predictability or controlability of the stimulus (Lejuez et al 2000, Mineka and Henderson 1985). In regard to the threat of pain, Bolles and Fanselow (1980) argued that the threat of pain elicited by explicit forewarning of its occurrence acts to inhibit pain at a perceptual stage, thus reducing its impact on central nervous system resources. Consistent with this proposal, Rhudy and Meagher (2000) showed decreased pain threshold caused by the threat of possible electric shock and increased pain threshold caused by a predictable and unavoidable electric shock. Those authors propose that the former induces anxiety (distress

related to some uncertain event) and the latter induces fear (distress related to an unavoidable danger). Bolles and Fanselow (1980) suggest that the reduced impact of a predictable and unavoidable painful stimulus is mediated by a conditioned endogenous analgesic mechanism; however such a mechanism is known to have slow recruitment and long recovery time (Matzel and Miller 1987). An alternative explanation is that the individual who knows a painful stimulus is possible but uncertain devotes more central nervous system resources to scanning the environment for further information and the individual who can be certain of the impending painful stimulus intentionally attends away from it. A final possibility is that different people respond in a different manner that is dependent on cognitive and emotional characteristics of each individual (Keogh et al 2001).

The aim of this study was to determine if disruption of central nervous system performance by the threat of impending pain is affected by whether the pain is unpredictable and possible or predictable and unavoidable. Thus, the hypotheses were (1) that reaction time is increased by the threat of an unpredictable but possible pain stimulus, and (2) that reaction time is not increased by a predictable and unavoidable painful stimulus.

## Method

***Participants*** Sixteen healthy participants (9 female) with a mean age of 29 ± 6 years, participated in the experiment. Subjects with diagnosed diabetes, any psychiatric disorder, sensory changes in hand/arm, or pain were excluded. Written informed consent was obtained. All procedures were approved by the institutional research ethics committee and conformed to the Declaration of Helsinki.

***Protocol*** A standard visuomotor reaction time task was used. Subjects responded by pushing a button with the index finger of the dominant hand as quickly as possible to a light that was placed 1.5 m in front of them. A random period (0.5 to 2 s) prior to each light, subjects received a verbal warning ("ready"). There were 20 trials in each condition. This number of trials was selected because pilot trials showed that it was insufficient to produce a conditioned fear response to the visual stimulus, as measured by galvanic skin response.

In a single session, a control trial was followed by experimental conditions presented in random order and then a second control trial. For the experimental conditions, noxious stimulation was delivered to the index finger of the non-dominant hand, 200 ms after the stimulus to move, either 100% of the time (predictable) or randomly 50% of the time (unpredictable).

***Determination of the perceptual and noxious stimuli*** Two surface EMG electrodes (Ag/AgCl discs, 1 cm diameter) were placed on the lateral and medial surface of the middle phalanx of the index finger of the non-dominant hand. The stimulus (60 Hz, 100 ms train, 1 ms pulse duration) was delivered with increasing intensity and the subject was instructed to indicate when the stimulus became "moderately painful". This level was designated the noxious stimulus.

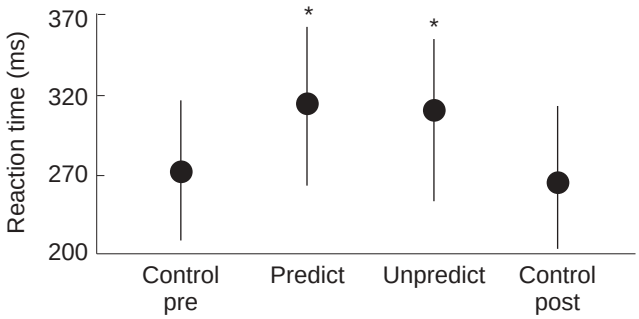


**Figure 1.** Mean and SDs for reaction time across conditions. Asterisks denote greater reaction time than during control ($p < 0.01$). Note that there is no effect of predictability of the painful stimulus.

***Fear, anxiety and physiological arousal*** Electrocardiographic activity (ECG) was recorded using a pair of surface electrodes (Ag/AgCl discs, 1 cm diameter) placed approximately 3 cm left of the 3rd left sternocostal joint. A ground electrode was placed over the clavicle. Heart rate was obtained from ECG data using Spike2 4.09[a]. Those frames in which two heartbeats were captured (~70% of frames) were used for analysis. Heart rate = 60/t, where t is the time in seconds between heartbeats. An average heart rate was determined for each subject for each condition. Subjective measures of fear and anxiety were obtained after each condition: using two separate 11 point numerical rating scales, each anchored with "not at all" and "extremely," subjects were asked "How fearful/anxious were you during those trials?"

***Statistical analysis*** All statistical procedures were performed in Statistica 5.1[b]. Mean reaction time from 20 trials was compared between the four conditions using a one way repeated measures ANOVA and Scheffé post-hoc testing, as were heart rate, reported fear and reported anxiety. Multiple linear regression analysis was conducted with reaction time as the dependent variable and heart rate and reported anxiety as the independent variables.

Individual data were also assessed because two contrasting patterns of effect would be concealed in a group analysis. Analysis of individual data was also conducted using one-way ANOVAs and Scheffé post-hoc testing. Although multiple measures elevate the probability of a type I error, a Bonferroni correction would elevate the probability of a type II error and reduce significance to $p < 0.003$, which we considered to be too conservative. Because the current work was exploratory in nature, and in light of criticism in the literature of Bonferroni and other corrections, eg Perneger (1998), we considered it appropriate to maintain significance at $p = 0.05$.

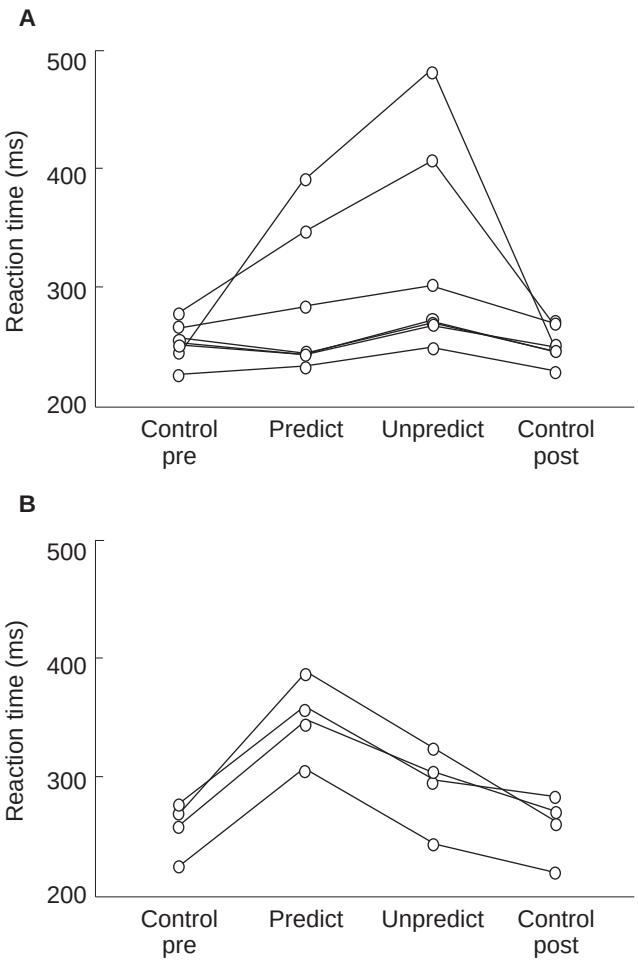


**Figure 2.** (A) Mean reaction times across conditions for individual subjects who had a greater ($p < 0.05$) increase in reaction time during the unpredictable condition (n = 8) and (B) those who showed the opposite effect ($p < 0.05$) (n = 4). Four subjects did not have a differential effect between conditions (data not shown).

## Results

***Reaction time data*** Figure 1 presents the group data for reaction time during control and experimental trials. There was an effect of condition ($p < 0.01$) and reaction time was greater in both experimental conditions than in either control condition ($p < 0.01$ for both). The effect 95% CI was 50 ms (16 to 83 ms) for predictable and 46 ms (12 to 80 ms) for unpredictable. There was no difference between the two experimental conditions (mean = 7ms, 95% CI -24 to 38ms, $p = 0.41$) or between the two control conditions ($p = 0.46$).

Two patterns emerged in the individual data, presented in Figure 2. In eight subjects, reaction time in the predictable condition was less than reaction time in the unpredictable condition (Figure 2A), and in four subjects the opposite pattern occurred (Figure 2B) ($p < 0.05$ for all). Four subjects demonstrated no difference between predictable and unpredictable conditions.

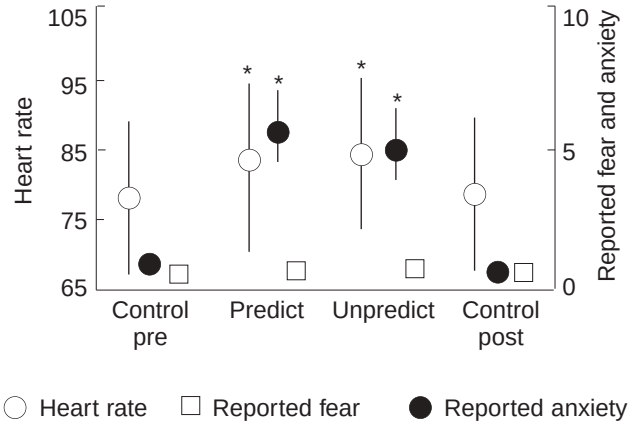


**Figure 3.** Mean and SDs for heart rate, reported fear, and reported anxiety across experimental conditions. Note no effect of experimental condition on reported fear. Asterisks denote greater than control ($p < 0.01$).

***Fear, anxiety and physiological arousal*** Figure 3 presents the heart rate, reported fear and reported anxiety level during the control and experimental conditions. There was an effect ($p < 0.001$); heart rate and reported anxiety were higher in the experimental conditions than in the control trials ($p < 0.001$) but were not different between the two experimental conditions ($p > 0.4$ for both). Subjects did not report being fearful (mean ± SD for experimental conditions 0.6 ± 1). The multiple regression analyses showed a moderate relationship between reported anxiety and reaction time (r = 0.49, $p = 0.004$), but no relationship between heart rate and reaction time or heart rate and anxiety ($p > 0.14$).

## Discussion

The results of this study support the first hypothesis that reaction time is increased by unpredictable and possible impending pain but do not support the second hypothesis that reaction time is unaffected by predictable and unavoidable pain. These conclusions are upheld by the group data that show a longer reaction time for both the predictable and unpredictable conditions than the control trials. Notably there was a moderate relationship between reaction time and reported anxiety across the group. Taken together, the findings suggest that perceived anxiety is an important factor in determining the extent to which the threat of pain disrupts stimulus processing and response.

Relevant to the current hypotheses was the notion that uncertain painful events induce anxiety whereas certain painful events induce fear (Rhudy and Meagher 2000), the latter possibly triggering an endogenous analgesic response (Bolles and Fanselow 1980). However in the current study subjects did not report fear of pain. This may represent a shortcoming of the experimental protocol or, alternatively, it may reflect difficulty in delineating between fear and anxiety. Either way, although this finding raises doubt about the semantics of unpredictable and predictable pain,

the main results of the study were not affected

Our findings are consistent with previous studies that used a primary task paradigm (Crombez et al 1994, Crombez et al 1996, Crombez et al 1997). Those studies demonstrated that the threat value of a painful stimulus was an important predictor of pain interference. They proposed that the threat of pain causes the central nervous system to devote resources to the object of threat for further investigation, which means that the disruption caused by pain would depend upon its initial threat value. The current study investigated more closely the impact of threat alone on central nervous system performance. We proposed that the individual who knows a painful stimulus is possible devotes more central nervous system resources to scanning the environment for further information and the individual who can be certain of the impending painful stimulus intentionally attends away from it. However, our results do not support this proposal: there was no group effect and the individual data showed a different pattern of effect in 50% of participants. Thus the predictability of the painful stimulus does not have an effect that is consistent across individuals. However, the anxiety associated with the threat of pain does seem to have a consistent effect. This is evidenced primarily by the correlation between reported anxiety and reaction time ($r = 0.47$, $p < 0.01$). The effect of anxiety on reaction time has been shown previously (Shiomi 1977, Stamps et al 1979).

The relationship between anxiety and reaction time, and the variable relationship between predictability and reaction time, may reflect the importance of controllability in determining the threat associated with an impending painful stimulus. That is, controllability may explain why for some individuals pain that is predictable may be more threatening than unpredictable pain, while for other individuals the opposite is true. This would be consistent with previous work that suggests that the stress associated with aversive events is mediated by the degree of control that the individual can impart over the stimulus, regardless of its predictability (Miller 1979, Tsuda et al 1989). In the current study, perhaps some individuals had a better control strategy in the unpredictable condition, while other individuals had a better control strategy in the predictable condition.

Previous studies have reported habituation of pain interference with repeated stimulation (Crombez et al 1997, Gewirtz and Davis 1995). We did not explicitly measure habituation; however, we did notice a trend towards a reduced effect with later trials in each experimental condition that may have been concealed by the small sample size used here, or may have occurred to a significant extent if more trials were performed. Further study should clarify this issue.

The findings of the current work should be considered in light of several limitations. First, we relied on subjective report to estimate anxiety about the impending pain. More information may have been gained using measures of physiological arousal such as galvanic skin response or endocrine markers, although variable time course of the latter may be problematic. We chose reported anxiety because the importance of *perceived* threat has been emphasised in the literature (Crombez et al 1998a). Importantly, there was no relationship between reaction time and heart rate, or heart rate and anxiety, even though a moderate relationship was observed between reaction time and perceived anxiety. Those findings suggests that reported anxiety was a suitable measure but that heart rate is not an appropriate physiological indicator, at least in this paradigm. A second limitation is that gender has been shown to have a significant effect on reaction time (Taimela and Kujala 1992) but the current study was underpowered to detect such an effect or its impact on the results. Third, experimentally induced pain by cutaneous shock does not accurately simulate clinical pain. However, the advantage of this method of inducing pain is that the timing and magnitude of the stimulus can be accurately controlled and the plethora of confounders associated with non-experimental pain can be removed. It was therefore the most appropriate strategy for the current study. Finally, the main results of this study may not be specific to impending pain, but rather may depend on the impending shock of receiving an electrical stimulus. Would similar effects be observed with impending noise? Habituation to such stimuli is far more rapid than that observed in the current experiment (Gewirtz and Davis 1995), which suggests that the noxious nature of the stimulus is probably important, but this possibility cannot be excluded.

The current findings are relevant from a clinical point of view because they suggest that when patients are anxious about an impending pain, central nervous system performance is reduced. This may be particularly pertinent to movement and postural reactions where the timing of motor responses is crucial and delays in the order of those observed here (~30 ms) may cause ongoing nociceptive stimulation (Hodges and Richardson 1996) and have been linked to increased injury rates (Taimela and Kujala 1992). Further studies are required to clarify these issues.

In summary, the current work found that the threat of pain disrupts central nervous system performance but the effect is not necessarily greater if the impending pain is unpredictable. Results from individual participants suggest that the predictability of the pain has different effects in different individuals, that the salient factor is the degree to which the condition induces anxiety about the impending pain and that this may be mediated by the controllability of the painful stimulus. The results are consistent with previous proposals that the threat value of pain determines its demand on central nervous system resources. Finally, the threat of pain alone may compromise central nervous system responses and place patients at risk of further or secondary injury.

***Footnotes*** [a]Cambridge Electronic Design, Cambridge UK. [b] Statsoft, Tulsa, USA

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