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Original Report

Endogenous Pain Modulation Induced by Extrinsic and Intrinsic Psychological Threat in Healthy Individuals

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Abstract: **Many factors interact to influence threat perception and the subsequent experience of pain. This study investigated the effect of observing pain (extrinsic threat) and intrinsic threat of pain to oneself on pressure pain threshold (PPT). Forty socially connected pairs of healthy volunteers were threat-primed and randomly allocated to experimental or control roles. An experimental pain modulation paradigm was applied, with non-nociceptive threat cues used as conditioning stimuli. In substudy 1, the extrinsic threat to the experimental participant was observation of the control partner in pain. The control participant underwent hand immersion in noxious and non-noxious water baths in randomized order. Change in the observing participant's PPT from baseline to mid- and postimmersion was calculated. A significant interaction was found for PPT between conditions and test time ($F_{2,78} = 24.9$, $P < .005$). PPT increased by 23.6% ± 19.3% between baseline and during hand immersion ($F_{1,39} = 43.7$, $P < .005$). Substudy 2 investigated threat of imminent pain to self. After a 15-minute break, the experimental participant's PPT was retested ("baseline 2"). Threat was primed by suggestion of whole arm immersion in an icier, larger water bath. PPT was tested immediately before anticipated arm immersion, after which the experiment ended. A significant increase in PPT between "baseline 2" and "pre-immersion" was seen ($t = -7.6$, $P = .005$), a pain modulatory effect of 25.8 ± 20.7%. Extrinsic and intrinsic threat of pain, in the absence of any afferent input therefore influences pain modulation. This may need to be considered in studies that use noxious afferent input with populations who show dysfunctional pain modulation.**

Perspectives: ***The effect on endogenous analgesia of observing another's pain and of threat of pain to oneself was investigated. Extrinsic as well as intrinsic threat cues, in the absence of any afferent input, increased pain thresholds, suggesting that mere threat of pain may initiate analgesic effects in traditional noxious experimental paradigms.***

Key words: *Endogenous analgesia, conditioned pain modulation, threat conditioning, pressure pain threshold, healthy participants.*

Pain is an essential protective mechanism, signaling threat of actual or potential tissue injury[22] and it is now well accepted that numerous biological, psychological, and contextual factors interact to influence the perception of threat and the experience of pain that emerges from this perception.[23] Fundamental to this is the understanding that the central nervous system can powerfully modulate input[29] enabling facilitation as well as inhibition of incoming information. This modulatory effect is commonly referred to as descending modulation.

It is well established that context, physiological, and psychological factors may influence pain modulatory responses in humans. Stress and exercise-induced analgesia are well described[5,24,25] and the descending modulation of pain seen with placebo is thought to be (in part) attributable to conditioning and expectation.[7] In addition,

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tonic noxious stimulation has also been shown to induce descending modulation in animals[17] and when applied to humans to induce a pain modulatory response.[15]

Pain modulation tested in response to a tonic noxious stimulus has been widely reported,[15,18,19,21,24] with a normal response seen as a decrease in nociceptive sensitivity. It appears that this response may be absent or even reversed in some individuals with chronic pain,[9,16,18] suggesting that alterations in modulatory capacity may contribute to some clinical presentations. In traditional paradigms, the noxious afferent input is provided by a tonically applied conditioning stimulus. A test stimulus is then used commonly to assess pain thresholds before and during conditioning stimulus application, with the difference being attributed to the pain modulatory effect.[35] However, it is unclear if disruption of this pain modulatory response in people with chronic pain is solely due to altered central nervous system response to the intense noxious somatosensory input or whether, and to what extent, other extrinsic or intrinsic factors are involved. Recent data have shown the role of cognitive factors in moderating the extent of the pain modulation response.[12] It must be acknowledged that any given pain experience may be modulated by psychological factors such as stress, expectation, and empathy.[3,10,11,24,27] However additional formal evaluation of the modulatory capacity of non-nociceptive forms of threat may be useful in our understanding of endogenous pain modulation mechanisms.

We were therefore interested in exploring whether extrinsic or intrinsic threat cues alone, in the absence of any somatosensory peripheral stimulation, were sufficient to engender a pain modulatory response in healthy individuals. In the first substudy, we investigated if close observation of a friend or partner experiencing a painful stimulus (extrinsic threat) would elicit a modulatory effect on a noxious test stimulus in the observer. This was immediately followed by the second substudy in which we investigated whether imminent threat to oneself by the same painful stimulus (intrinsic threat) modulated the same noxious test stimulus. It was hypothesized that healthy participants would show a pain modulatory effect in response to extrinsic as well as intrinsic threat cues.

Methods

Participants

Forty pairs of healthy, pain-free adult volunteers, aged between 18 and 60 years were recruited from staff and students at the University of Notre Dame Australia, via notice board advertisements, social media, and word of mouth. Because of the observational nature of study 1 participant pairs with strong social relationships were specifically sought.

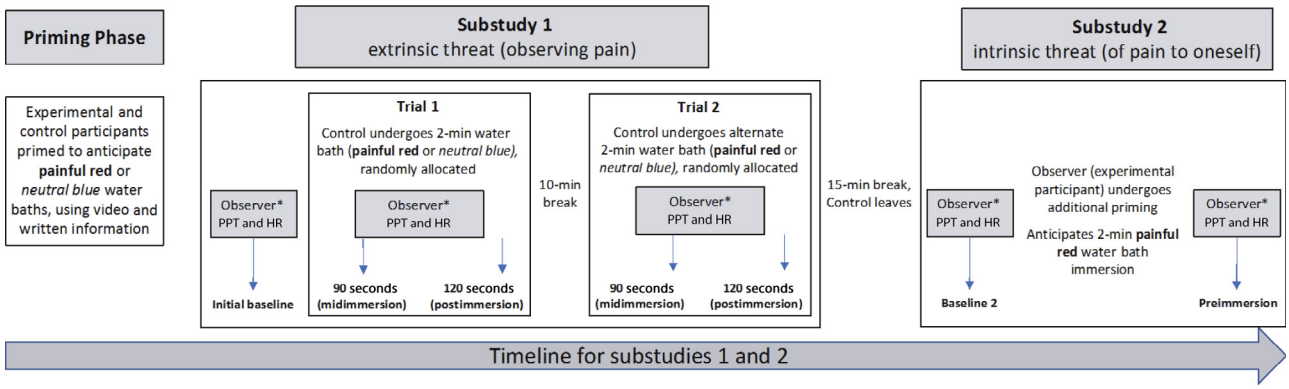
Participants were eligible if they were fluent in written and spoken English and were able to provide informed consent. Participants were excluded if they reported any current major medical condition or chronic pain disorder, were taking any pain medication, reported any previous surgery or major trauma in the test areas, reported excessive sensitivity to cold, or had experienced any significant pain problem within the past 12 months. Volunteers were screened for eligibility via phone and provided with information about the study via e-mail. Ethical approval was provided by the University of Notre Dame Australia Human Research Ethics Committee (approval 014174F). Written informed consent was obtained from all subjects before testing and all procedures conformed to the Declaration of Helsinki.

Procedure

The study was divided into 3 parts: a priming phase (which occurred before testing), then substudies 1 (extrinsic threat: observing pain) and 2 (intrinsic threat of pain to oneself), which occurred consecutively in the same test session (Fig 1). Although pairs of participants were recruited, only 1 individual underwent both threat conditioning studies. This individual was randomly selected after the priming phase. Both participants remained blind until substudy 2 was completed. For clarity, the participants will be termed "experimental participant" and "control participant."

Priming Phase

Study 2 (intrinsic threat) depended on the participant expecting red colored water immersion to be painful.



PPT - pressure pain threshold; HR - heart rate; * "Observer" indicates experimental participant

Figure 1. Testing protocol for substudies 1 and 2. * "Observer" indicates experimental participant.