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The importance of context: When relative relief renders pain pleasant

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ABSTRACT

Context can influence the experience of any event. For instance, the thought that "it could be worse" can improve feelings towards a present misfortune. In this study we measured hedonic feelings, skin conductance, and brain activation patterns in 16 healthy volunteers who experienced moderate pain in two different contexts. In the "relative relief context," moderate pain represented the best outcome, since the alternative outcome was intense pain. However, in the control context, moderate pain represented the worst outcome and elicited negative hedonic feelings. The context manipulation resulted in a "hedonic flip," such that moderate pain elicited positive hedonics in the relative relief context. Somewhat surprisingly, moderate pain was even rated as *pleasant* in this context, despite being reported as painful in the control context. This "hedonic flip" was corroborated by physiological and functional neuroimaging data. When moderate pain was perceived as pleasant, skin conductance and activity in insula and dorsal anterior cingulate were significantly attenuated relative to the control moderate stimulus. "Pleasant pain" also increased activity in reward and valuation circuitry, including the medial orbitofrontal and ventromedial prefrontal cortices. Furthermore, the change in outcome hedonics correlated with activity in the periacqueductal grey (PAG) of the descending pain modulatory system (DPMS). The context manipulation also significantly increased functional connectivity between reward circuitry and the PAG, consistent with a functional change of the DPMS due to the altered motivational state. The findings of this study point to a role for brainstem and reward circuitry in a context-induced "hedonic flip" of pain.

1. Introduction

Pain from nociception is considered intrinsically aversive [42]. Nonetheless, anecdotal evidence suggests that even strong noxious stimulation is sometimes pleasurable, as for spicy food or in the case of sexual masochism [37]. Pleasure and pain are often represented as opposites within a hedonic spectrum [7,13,48], and can have mutually inhibitory effects [36]. These feelings induce competing motivational states that alter the function of the descending pain modulatory system (DPMS) [18]. In line with the view of pain and pleasure as opposites, we have previously shown that safety from pain causes a pleasant feeling of relief [34]. Furthermore, we and others have demonstrated that relief from pain activates reward and valuation circuitry such as the ventral striatum and the ventromedial prefrontal/orbitofrontal cortices (vmPFC/OFC) [3,35,53].

It is well established that neural activity often reflects the *relative* rather than the *absolute* value of events across different contexts [52]. For instance, losing money usually causes negative feelings. However, in a context where all alternative outcomes are larger losses, losing a small amount can elicit positive emotions (relative relief) and activation in ventral striatum and vmPFC/OFC [11,29,41,43,61]. Similarly, macaque orbitofrontal neurons encoded the preferred reward in a reward context, and encoded relative safety (no stimulus) in an aversive context in which the alternative outcome was electric shock [23].

The present study investigated the effects of relative relief on hedonic and physiological reactions to moderate pain. We used a context manipulation to alter the relative value of a moderately painful stimulus. In the control context, the alternative outcome was nonpainful warmth. Thus, the moderately painful stimulus was the worst possible outcome, akin to how pain is commonly perceived in laboratory and real-life settings. In contrast, in the "relative relief context," the alternative outcome was an intensely painful stimulus. The moderately noxious stimulus, which was identical across the two contexts, was therefore the better of the

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two possible outcomes and represented relative relief. This design ensured that the moderate pain stimuli in the two contexts were matched for surprise as well as intensity, timing, and frequency of nociceptive input. We measured the hedonics, skin conductance response, and functional magnetic resonance imaging (fMRI) signal associated with moderate pain across these two contexts in 16 healthy volunteers.

We hypothesised that the context manipulation would result in a *hedonic flip*, such that the normally aversive, moderate pain would elicit more positive hedonics and higher activity in reward circuitry including the ventral striatum and vmPFC/OFC. Consequently, since reward system activity inhibits pain [22,36,72], we expected diminished skin conductance and fMRI signal responses within key regions of the brain's pain network [1,2]. We hypothesised that this relief-related analgesic response would recruit the DPMS (eg, [9,59,64,70,71]). Finally, we expected the relative relief context to induce an affectively and motivationally distinct state in participants. Since the function of the DPMS is state dependent, we hypothesised that this state change would be reflected in alterations in the connectivity pattern of the DPMS, specifically the periacqueductal grey (PAG) [18,19].

2. Methods

2.1. Participants

Seventeen right-handed healthy volunteers (mean age 25 years, age range 19-41 years, 8 females) were recruited for this study. All participants gave written informed consent, and none had contraindications to MRI. The study was approved by the Central Oxfordshire Clinical Research Ethics Committee (C02.286) and conforms to the guidelines of the Declaration of Helsinki (1996). Participants were reimbursed 25 GBP. One participant's dataset was incomplete due to technical difficulties. This participant was excluded from analysis, yielding a final n = 16.

2.2. Study design

The study design is outlined in Fig. 1. The study consisted of two functional MRI scanning sessions of 15 minutes each, separated by a 10-minute structural MRI scan. The order of the two sessions (relative relief session and control session) was counterbalanced across participants. Each session consisted of 24 trials, each lasting ~36 seconds. Each trial consisted of: 1) a 50% predictive visual cue presented for 6 seconds; followed immediately by 2) heat stimulation for 4 seconds; and finally, 9 seconds after heat offset, 3) a 6-second rating period, where a visual analogue scale (VAS) was presented. After a 13-second interval, another trial began with a new presentation of the visual cue. This interval ensured that the onset of each trial was jittered with respect to the 3-second repetition time (TR). Trial order was pseudorandomised within each session. Before the scan, participants viewed a slideshow explaining what would occur during the study.

In the control session, we used the predictive visual cue (warm cue) to induce expectation of innocuous heat. The warm cue consisted of a green screen and white text ("Warm stimulus coming up..."). In 50% of the trials, the warm cue remained on the screen after the 6-second anticipation period, and during the 4-second innocuous warm thermal stimulation. In the remaining trials, the warm cue was replaced after 6 seconds by a black screen with a white arrow pointing upwards (up arrow), signaling the occurrence of a higher temperature, noxious outcome (the "control moderate"). This visual cue co-occurred with a thermal stimulus calibrated to induce moderate pain.

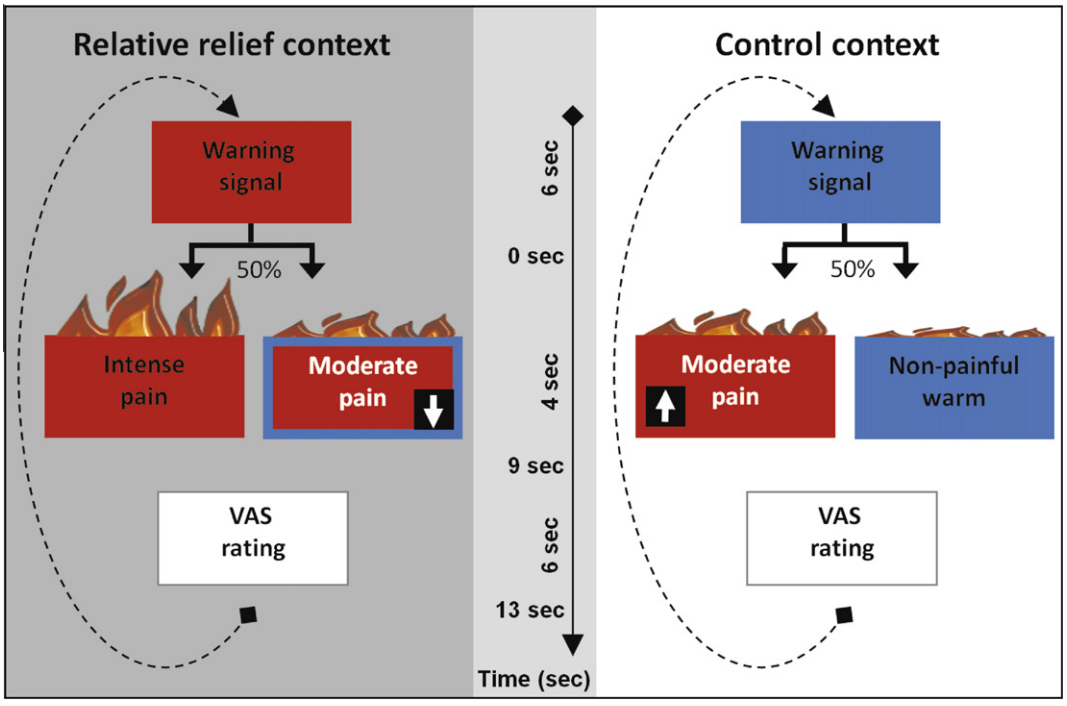

Fig. 1. Experimental design. The same moderately painful stimulus was presented in two different contexts (sessions). In the relative relief context, participants were cued to expect a high proportion of intensely painful stimuli. They were informed that in some instances, the warning signal would be replaced by an arrow pointing down, indicating that a lower temperature would be applied to the skin (relative relief). In the control context, participants were cued to expect nonpainful warm stimuli, but were informed that the warning signal would sometimes be followed by a higher temperature, as indicated by an arrow pointing upwards. Thus, the moderate pain stimulus was the worst possible outcome in the control context, akin to how pain is commonly perceived in laboratory and real-life settings. The moderately noxious stimulus was identical across the two contexts, its temperature selected to elicit moderate pain in each individual before the scan. In both contexts, the moderate pain stimuli were 50% probable, and session and stimulus presentation orders were counterbalanced. VAS, visual analogue scale.