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From Pavlov to pain: How predictability affects the anticipation and processing of visceral pain in a fear conditioning paradigm

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ABSTRACT

Conditioned pain-related fear may contribute to hyperalgesia and central sensitization, but this has not been tested for interoceptive, visceral pain. The underlying ability to accurately predict pain is based on predictive cue properties and may alter the sensory processing and cognitive–emotional modulation of pain thus exacerbating the subjective pain experience. In this functional magnetic resonance imaging study using painful rectal distensions as unconditioned stimuli (US), we addressed changes in the neural processing of pain during the acquisition of pain-related fear and subsequently tested if conditioned stimuli (CS) contribute to hyperalgesia and increased neural responses in pain-encoding regions. $N = 49$ healthy volunteers were assigned to one of two groups and underwent 3T fMRI during acquisition of either differential fear conditioning (predictable) or non-contingent presentation of CS and US (unpredictable). During a subsequent test phase, pain stimuli signaled randomly by the CSs were delivered. For the acquisition, results confirmed differential conditioning in the predictable but not the unpredictable group. With regard to activation in response to painful stimuli, the unpredictable compared to the predictable group revealed greater activation in pain-encoding (somatosensory cortex, insula) and pain-modulatory (prefrontal and cingulate cortices, periaqueductal grey, parahippocampus) regions. In the test phase, no evidence of hyperalgesia or central sensitization was found, but the predictable group demonstrated enhanced caudate nucleus activation in response to CS^--signaled pain. These findings support that during fear conditioning, the ability to predict pain affects neural processing of visceral pain and alters the associative learning processes underlying the acquisition of predictive properties of cues signaling pain, but conditioned pain-related fear does not result in visceral hyperalgesia or central sensitization.

Introduction

From an evolutionary perspective, the ability to accurately predict pain is crucial for survival. Consequently, learning to predict pain based on predictive signals can be considered a fundamental and highly adaptive process, which allows the organism to evoke a range of complex responses aimed at self-protection or avoidance. Fear conditioning as a translational model in the neurosciences has proven indispensable in elucidating associative learning processes involving aversive stimuli, including pain, as a uniquely aversive and highly salient experience (Vlaeyen, 2015). As a result of contingent pairing of pain-predictive conditioned cues (CS^+) with painful unconditioned stimuli (US), differential conditioned responses can be evoked by presentation of the pain-predictive CS^+ when compared to another cue that remains unpaired (CS^-). In addition to pain-related fear as the most prominent response, pain-predictive CS may come to evoke a range of reactions, including increased arousal and selective attention. At the same time, cues signaling safety from pain may further reinforce safety seeking and avoidance behaviors. Hence, by acquiring specific predictive properties, the interplay of conditioned danger and safety signals could play a role in the transition from acute to chronic pain by contributing to hypervigilance and hyperalgesia (Vlaeyen, 2015).

Altered fear conditioning has been reported in several chronic pain conditions (Meulders et al., 2015; Nees et al., 2010), including chronic visceral pain, as it characterizes the irritable bowel syndrome (IBS) (Icenhour et al., 2015a; Labus et al., 2013a). However, knowledge about the role of pain predictability in shaping pain-related neural processes remains scarce even in healthy volunteers. Previous fear conditioning studies outside the pain field revealed differences between continuous and intermittent CS–US pairings on brain responses to the CS (Dunsmoor et al., 2007) as well as correlations between affective

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state and neural responses to predictable and unpredictable threat (Harnett et al., 2015). Our previous work in the visceral pain field focused exclusively on differential responses to the CS (Gramsch et al., 2014; Icenhour et al., 2015b; Kattoor et al., 2013) without specific attention to the US. If the neural processing of pain as US is affected by its predictability during different phases of fear conditioning remains unclear. Existing studies employing other types of aversive US support that US expectancies affect the magnitude of the unconditioned response (Knight et al., 2010; Wood et al., 2012, 2013, 2015). Therefore, our first goal was to address effects of predictability on changes in the neural processing of the CS and US during the acquisition of visceral pain-related fear. To do so, we compared a group who underwent differential fear conditioning with rectal distension as predictive painful US (predictable group) and a group who received the identical number of stimuli presented in non-contingent manner (unpredictable group). In our analysis, we compared these groups with respect to differences in CS- and US-related BOLD responses with a focus on pain-encoding and pain-modulatory brain regions.

Furthermore, with one exception using somatic pain as US (Williams and Rhudy, 2007), it has not been tested if conditioned pain-related fear contributes to visceral hyperalgesia. Therefore, the second aim was to test if conditioned fear of pain, once established, leads to visceral hyperalgesia and increased visceral pain-induced BOLD responses in pain-encoding regions. This hypothesis was built on evidence from conditioning with somatic pain stimuli that fear conditioning may lower pain thresholds (Williams and Rhudy, 2007), contribute to nocebo hyperalgesia involving conscious as well as unconscious processes (Colloca and Benedetti, 2007; Jensen et al., 2012a, 2014, 2015), involving higher perceived threat and attention to pain as a function of predictability (Lin et al., 2014; Vlaeyen, 2015). To do so, subsequent to the acquisition phase, we implemented a test phase identical for both groups, which consisted of repeated CS-cued presentations of painful visceral stimuli such that the cues were fully predictive of pain. To address within- and between-group differences, we compared pain stimuli signalled by cues that were either formerly conditioned danger or safety cues (in the predictable group) or had no differential predictive cue properties (in the unpredictable group) and accomplished trial-by-trial VAS ratings after each pain stimulus. At the level of BOLD responses, we then compared pain processing between CS^+- versus CS^--signalled pain stimuli.

Methods

Participants

A total of 49 healthy young adults (25 females, 24 males) were recruited by local advertisement. Inclusion criteria were an age range between 18 and 45 years, a body mass index (BMI) in the range of 18 to 27, no concurrent medical condition, including any history of gastrointestinal conditions except appendicitis, relevant upper or lower gastrointestinal symptoms, evidence of external and internal anal tissue damage (e.g., painful hemorrhoids which may interfere with balloon placement), and acute or chronic somatic, psychiatric, or psychological diseases based on self-report or any concurrent regular medication use. We also assessed anxiety and depression scores by means of the Hospital Anxiety and Depression Scale (HADS) (Herrmann-Lingen et al., 2005) and used the published criteria to exclude participants above the clinically relevant cutoff (i.e., ≥8). Frequency and severity of gastrointestinal complaints suggestive of any functional or organic gastrointestinal condition were assessed with a standardized in-house questionnaire (Lacourt et al., 2014) and personal interview. We excluded naturally cycling females to reduce potential confounding by menstrual cycle phase. Pregnancy was routinely excluded by commercially available urinary test on the day of study participation. The study protocol followed the rules stated in the Declaration of Helsinki and was approved by the local Ethics Committee of the University Hospital Essen at the University of Duisburg-Essen, Germany. All participants gave written informed consent and were reimbursed for participation. Participants were informed that the aim of the study was to address visceral pain-related learning processes, but no further specific instructions were given.

Study design and procedures

Each participant completed the study protocol within one study day with a total duration of approximately 1.5 h. Due to irregular availability of the scanner, time of day was not standardized. Given high inter-individual variations in rectal pain sensitivity in healthy volunteers (Elsenbruch et al., 2014), we individualized stimulus intensities (i.e., rectal distension pressures) for US application as previously established (Gramsch et al., 2014; Kattoor et al., 2013; Icenhour et al., 2015a, 2015b). To do so, individual rectal sensory and pain thresholds were first determined outside the scanner with a pressure-controlled barostat system (modified ISOBAR 3 device, G and J electronics, Ontario, Canada). The thresholding procedure consisted of a double-random staircase distention protocol with random pressure increments of 2 until 10 mmHg with a limit of maximal distension pressure set at 50 mmHg. Participants were asked to rate each sensation on a scale labeled with "1" indicating no pain perception, "2" as doubtful perception, "3" as sure perception," "4" as little discomfort, "5" as severe discomfort, and "6" indicating not tolerable pain. The threshold for first pain perception was determined at the ascent from "2" to "3" and the individual pain threshold at the ascent from "5" to "6." To avoid intolerable pain intensities during repeated distensions in the scanner, we subtracted 2 mmHg from the individual pain threshold.

Subsequently, participants were randomly assigned either to the predictable or unpredictable group, operationalized through different contingencies of CS–US pairings. Whereas the predictable group underwent a classical fear conditioning paradigm (Kattoor et al., 2013; Icenhour et al., 2015a, 2015b), the unpredictable group received non-contingently presented stimuli. Afterwards, the scanning procedure started with a structural MRI followed by event-related fMRI, measuring the neural activation during the anticipation and delivery of painful visceral stimuli in three consecutive scanning sessions, i.e., acquisition, pain test phase, and extinction phase (for details, see section conditioning protocol). During all sessions, visual cues served as CS (e.g., circle and rectangle randomly used as CS^+ or CS^-) and painful rectal distensions were used as unconditioned stimulus (US). After each scanning session, participants were asked to rate CS pleasantness (ranging from "−100" indicating very pleasant to "+100" indicating very unpleasant with 0 mm indicating neutral) and additionally, after the acquisition phase perceived CS–US contingency (ranging from "0%" to "100%") and overall painfulness of all US applied during acquisition (ranging from "0" to "100") using visual analogue scales (VAS). All visual stimuli and online rating scales were presented with Presentation® software (Neurobehavioral Systems, Albany, CA, USA), and ratings were accomplished with a hand-held fiber optic response device (LUMItouch™, Photon Control Inc., Burnaby, BC, Canada).

Paradigm

(A) Acquisition phase
As illustrated in Fig. 1A, in the acquisition phase, a total of 32 visual cues (i.e., 16 circles, 16 rectangles) and 12 painful rectal distensions were presented. For both groups, the sequence of visual cues remained equal but differed according to the delivery of US. In the classically conditioned, predictable group, the established conditioning protocol was implemented (Icenhour et al., 2015a, 2015b) involving contingent pairings of one visual cue (i.e., the CS^+) with painful distensions as US, while a second visual cue (CS^-) was presented without US (differential delay conditioning with a 75% reinforcement schedule, see Fig. 1 A top row). The