Neurobiology of Learning and Memory 116 (2014) 36–45

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Learning pain-related fear: Neural mechanisms mediating rapid differential conditioning, extinction and reinstatement processes in human visceral pain

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ARTICLE INFO

Article history:
Received 21 February 2014
Revised 14 July 2014
Accepted 6 August 2014
Available online 13 August 2014

Keywords:
Fear conditioning
Extinction
Reinstatement
Visceral pain
Irritable bowel syndrome
Functional magnetic resonance imaging

ABSTRACT

Background and aims: There exists converging evidence to support a role of pain-related fear in the pathophysiology and treatment of chronic pain conditions. Pain-related fear is shaped by associative learning and memory processes, which remain poorly characterized especially in the context of abdominal pain such as in irritable bowel syndrome (IBS). Therefore, using event-related functional magnetic resonance imaging (fMRI), we assessed the neural mechanisms mediating the formation, extinction and reinstatement of abdominal pain-related fear in healthy humans. Employing painful rectal distensions as clinically-relevant unconditioned stimuli (US), in this fear conditioning study we tested if differential excitatory and inhibitory learning is evocable after very few CS–US learning trials ("rapid conditioning"), and explored the underlying neural substrates of these learning and memory processes.

Methods: In $N = 24$ healthy men and women, "rapid" fear acquisition was accomplished by pairing visual conditioned stimuli (CS^+) with painful rectal distensions as unconditioned stimuli (US), while different visual stimuli (CS^-) were presented without US (differential delay conditioning with five CS^+ and five CS^- presentations and a 80% reinforcement ratio). During extinction, all CS were presented without US. Subsequently, a reinstatement procedure was implemented, defined as the retrieval of an extinguished memory after unexpected and unpaired exposure to the US, followed by CS presentations. For each phase, changes in perceived CS–US contingency and CS unpleasantness were assessed with visual analogue scales and compared with analyses of variance. fMRI data were analyzed using whole-brain analyses (at $p < .001$ uncorrected) and in regions-of-interest analyses with familywise error correction of alpha ($p_{FWE} < .05$). Differential neural activation in response to the CS during each experimental phase (i.e., $CS^+ > CS^-$; $CS^+ < CS^-$) was analyzed without and subsequently also with a linear parametric modulation including trial number as a regressor.

Results: A significant valence change (i.e. increased CS^+ unpleasantness) was observed following acquisition, indicating successful differential aversive learning. On the other hand, CS–US contingency awareness was not fully established. These behavioral results were paralleled by differential activation of the putamen ($p_{FWE} < .05$), insula ($p_{FWE} < .05$) and secondary somatosensory cortex (S2, $p < .001$ uncorrected) in response to the CS^+ during acquisition. The same analysis with a linear parametric modulation confirmed but also strengthened the resulting activations, which were all highly significant in ROI analyses at $p_{FWE} < .05$. Extinction and reinstatement involved differential activation in response to the CS^-, involving the cingulate cortex and primary motor cortex (M1) during extinction and the posterior cingulate cortex (PCC) during reinstatement (all $p < .001$ uncorrected), without obvious effects upon linear parametric modulation analysis.

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http://dx.doi.org/10.1016/j.nlm.2014.08.003

Conclusions: Abdominal pain stimuli are effective US that elicit conditioned pain-related fear even after very few learning experiences without full contingency awareness. These findings extend similar evidence of "rapid learning" in response to interoceptive US (e.g., conditioned taste aversion, conditioned nausea), and have implications for the pathophysiology and treatment of chronic abdominal pain such as in IBS.

1. Introduction

There exists converging evidence supporting a role of associative learning and memory processes in the development, maintenance and treatment of chronic pain states (Craske et al., 2011; De Peuter, Van Diest, Vansteenwegen, Van den Bergh, & Vlaeyen, 2011; den Hollander et al., 2010; Klinger et al., 2010; Nees et al., 2010; Schneider, Palomba, & Flor, 2004). Despite the high prevalence and clinical relevance of chronic abdominal pain, such as in irritable bowel syndrome (IBS), knowledge about the neural mechanisms involved in pain-related emotional learning and memory processes in clinically-relevant abdominal pain models (e.g., esophageal, gastric or rectal distensions) is limited, especially in humans (Elsenbruch, 2011; Kennedy et al., 2012; Stockhorst, Enck, & Klosterhalfen, 2007). Pavlovian fear conditioning paradigms are generally well-characterized with respect to the underlying neural mechanisms, involving brain regions considered part of the central "fear network", including the amygdala during acquisition, and hippocampal-prefrontal regions during extinction learning and memory retrieval (Sehlmeyer et al., 2009). Fear conditioning, as a translational model in the behavioral neurosciences (Milad & Quirk, 2012), has primarily been carried out in the context of anxiety (Hermans, Craske, Mineka, & Lovibond, 2006; Lissek et al., 2009, 2010), but may also be useful in the context of chronic abdominal pain given the well-documented overlap between pain and anxiety, especially in IBS (North, Hong, & Alpers, 2007), and the putative role of pain-related fear in the pathophysiology and maintenance of chronic pain (De Peuter et al., 2011; den Hollander et al., 2010; Zale, Lange, Fields, & Ditre, 2013). Indeed, from an evolutionary standpoint, the ability to discriminate and associate situations or cues that predict the occurrence of abdominal pain can be extremely important to allow effective survival strategies, such as avoidance of specific foods or contexts indicating the presence of bacterial or viral challenges. Hence, associative learning involving aversive visceral stimuli is almost certainly preserved across species and can be considered a fundamental learning process that remains poorly understood. Thus far, only very few conditioning studies employing esophageal (Yágüez et al., 2005) or rectal (Benson et al., 2014; Kattoor et al., 2013) pain as unconditioned stimuli (US) and visual cues as conditioned stimuli (CS) documented the feasibility and applicability of fear conditioning paradigms on the field of visceral pain. Most recently, altered conditioned neural responses during emotional learning and extinction were demonstrated in IBS patients (Labus et al., 2013). Herein, we aimed to complement and extend existing knowledge regarding the neural mechanisms mediating rectal pain-related learning and memory processes in healthy humans. Based on our previous fear conditioning study employing painful rectal distensions as clinically-relevant US (Kattoor et al., 2013), in this follow-up functional magnetic resonance imaging (fMRI) study we aimed to assess if differential aversive learning is already evocable after very few CS–US pairings ("rapid conditioning"). The rationale was that visceral pain-related fear conditioning may occur after very few learning experiences, as has previously been demonstrated in the context of conditioned taste aversion and conditioned nausea (Stockhorst et al., 2007). In order to accomplish this, we utilized the established fear conditioning paradigm, but implemented only five CS^+/five CS^- presentations with a 80% reinforcement ratio instead of previously 12 CS^+–US pairings (Kattoor et al., 2013) in the acquisition phase. We additionally aimed to characterize the neural mechanisms mediating extinction learning and reinstatement processes reflecting re-activation of learned fear in this rapid conditioning protocol. To do so, we presented only CS in an extinction phase, followed by a reinstatement procedure, defined as CS presentations subsequent to unexpected and unpaired exposure to the US (Rescorla & Heth, 1975). Together with renewal and spontaneous recovery paradigms, reinstatement is an experimental technique that provides an important tool to understand the mechanisms of memory formation and consolidation (Hermans et al., 2005; LaBar & Phelps, 2005) with interesting implications for pain-related fear memories that may be capable of triggering brain regions involved in the amplification of painful stimuli contributing to pain chronicity (Kelly, Lloyd, Nurmikko, & Roberts, 2007; Shimo et al., 2011). Given this background, our goal was to address behavioral and neural correlates of differential aversive learning and memory processes for abdominal pain-related fear in an experimental paradigm with very few CS–US pairings during acquisition ("rapid conditioning"). We tested the following specific hypotheses: (1) As a result of "rapid conditioning", emotional responses to the CS^+ compared to the CS^-, assessed with valence ratings, differ significantly as a result of contingent pairing with the US. Of note, we aimed to explore the question whether these learned emotional responses would be paralleled by full contingency awareness. (2) At the neural level, we expected differential activation in response to the CS^+ when compared to the CS^- in brain structures that participate in the processing of the CS and US, including the somatosensory cortices, insula, cingulate cortex and precuneus. Note that since we previously documented amygdala activation only during the late acquisition phase in a paradigm with more CS–US pairings (Kattoor et al., 2013), we did not expect differential amygdala activation herein. (3) For the extinction phase, we expected full extinction at the behavioral level (i.e., valence and contingency ratings), paralleled by activation of prefrontal regions, including the dorsolateral prefrontal cortex. (4) Finally, we tested the hypothesis that reinstatement would result in differential hippocampal activation in response to the CS^+ when compared to the CS^-.

2. Methods

2.1. Participants

Healthy volunteers were recruited by local advertisement. General exclusion criteria included age <18 years or >45 years, body mass index (BMI) < 18 or >27, any concurrent medical condition, anal tissue damage (e.g., painful hemorrhoids) and a history of psychological/psychiatric conditions (based on self-report) or scores above the published cut-offs (i.e., $\geqslant 8$) for mild-to-moderate symptoms of depression and/or anxiety, respectively, on the Hospital Anxiety and Depression Scale (HADS) (Herrmann-Lingen et al., 2005), evidence of structural brain abnormality upon structural