



Towards understanding sex differences in visceral pain: Enhanced reactivation of classically-conditioned fear in healthy women



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ABSTRACT

Sex differences in learned fear regarding aversive gastrointestinal stimuli could play a role in the female preponderance of chronic abdominal pain. In a fear conditioning model with rectal pain as unconditioned stimulus (US), we compared healthy males and females with respect to neural responses during aversive visceral learning, extinction and re-activation of fear memory (i.e., reinstatement). To do so, conditioned visual stimuli (CS⁺) were consistently paired with painful rectal distensions as US, while different visual stimuli (CS⁻) were presented without US. During extinction, both CSs were presented without US, whereas during reinstatement, a single, unpaired US was presented. In region-of-interest analyses, sexes were compared with respect to conditioned anticipatory neural activation (CS⁺ > CS⁻). The results revealed that in late acquisition, CS⁺ presentation induced significantly greater anticipatory activation of the insula in women. During extinction, women demonstrated reduced activation of the posterior cingulate cortex. During reinstatement, the CS⁺ led to greater activation of the hippocampus and cerebellum in women. These group effects in neural activation during learning and memory processes were not accounted for by sex differences in pain thresholds, pain ratings, or stress parameters. In conclusion, this is the first study to support sex differences in neural processes mediating aversive visceral learning. Our finding of enhanced neural responses during reinstatement in key brain areas relevant for memory suggests enhanced reactivation of old fear memory trace in women. Sex differences in “gut memories” could play a role in the female preponderance of chronic abdominal pain.

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1. Introduction

Women are more vulnerable not only to mood disorders but also to virtually all types of chronic pain conditions (Mogil, 2012). The functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), constitute one group of pain conditions with a marked female preponderance (Chang et al., 2006). The mechanisms underlying this female predominance are incompletely understood and likely encompass biological and psychosocial factors (Elsenbruch, 2011; Kennedy et al., 2012). Brain mechanisms unequivocally play a role in the pathophysiology of functional gastrointestinal disorders, as evidenced by findings in patient cohorts documenting the relevance of adverse life events, early life trauma, chronic stress, coexisting psychiatric disorders, and psychosocial predictors of IBS after acute gastroenteritis infectious (Chaloner & Greenwood-van Meerveld, 2013; Elsenbruch, 2011; Kennedy et al., 2012). However, the putative role of brain mechanisms in sex differences remains unclear in the context of

visceral pain, and the number of brain imaging studies analyzing sex differences in the neural processing of visceral pain remains limited (Benson et al., 2012; Berman et al., 2000, 2006; Kern et al., 2001; Labus et al., 2008; Naliboff et al., 2003).

Associative learning and memory processes have thus far rarely been studied in visceral pain (den Hollander et al., 2010; Yáguez et al., 2005). Fear conditioning is an established model in the context of anxiety disorders (Hermans, Craske, Mineka, & Lovibond, 2006; Hermans et al., 2005; Lissek et al., 2009, 2010; Milad & Quirk, 2012). Previous studies have also suggested a role of fear conditioning in the context of chronic pain (Klinger et al., 2010; Nees et al., 2010; Schneider, Palomba, & Flor, 2004). During fear conditioning, a neutral stimulus is repeatedly paired with an aversive unconditioned stimulus (US). As a result, the previously neutral stimulus turns into a predictive cue that is now a fear-provoking conditioned stimulus (CS) even when presented alone. Interestingly, this learned fear memory does not “disappear” during extinction but is rather preserved within the brain. Extinction is conceptualized as a form of new, inhibitory learning (Tronson, Corcoran, Jovasevic, & Radulovic, 2012), and given specific circumstances including reinstatement and renewal, the old fear memory

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can be re-activated (Bouton, 2004; Hermans et al., 2005, 2006; LaBar & Phelps, 2005; Myers & Davis, 2002). Thus far, only few studies have addressed sex differences in fear conditioning (Lebron-Milad et al., 2012; Merz et al., 2010, 2012). Two recent studies analyzed sex differences in pain-related fear conditioning employing painful electric stimulation and found pronounced responses in nociceptive flexion reflex magnitudes within an unpredictable threatening context in women (Hubbard et al., 2011) and sensitization over repeated conditioning blocks only in women (Meulders, Vansteenwegen, & Vlaeyen, 2012).

Until recently, visceral stimuli from the lower gastrointestinal tract were not established as aversive US. However, elucidating sex differences in associative learning and memory processes in the context of visceral pain using a conditioned fear model may contribute to understanding the female predominance of functional gastrointestinal conditions. Based on a seminal study using esophageal pain as US (Yáñez et al., 2005), we recently implemented the first fear conditioning study with painful rectal distensions as US in healthy subjects (Kattoor et al., 2013). Herein, we present results from an extension of this study testing sex differences in the neural processes mediating aversive visceral learning, extinction and the return of fear, i.e., reinstatement. We expected greater activation of brain regions mediating the affective-emotional aspects of fear learning and extinction, including the amygdala and anterior cingulate cortex, in women (Lebron-Milad et al., 2012). In addition, we hypothesized that women would show enhanced reactivation of the memory trace during reinstatement in brain regions mediating memory consolidation and retrieval, including hippocampal and prefrontal regions (Kennedy et al., 2012). To assess possible sex-specific effects of anxiety or stress (Merz et al., 2010), we also assessed tension along with salivary cortisol concentrations at different time points.

2. Methods

2.1. Recruitment, inclusion and exclusion criteria

Thirty healthy males and females (15 males; 15 females) matched by age (± 2 years) were recruited by local advertisement. Nineteen of the participants (6 females) were included in our previously published initial analysis which was conducted without attention to sex differences (Kattoor et al., 2013). For the purpose of this report, the sample size was increased to a final sample of $N = 15$ age-matched pairs. One male subject was excluded after completion of data acquisition due to movement artifacts. Of note, there was no overlap between subjects in the present study and those who participated in a previously published study on sex differences in visceral pain (Benson et al., 2012). General exclusion criteria included body mass index (BMI) < 18 or > 27 , any concurrent medical condition, structural brain abnormality, anal tissue damage (e.g., painful haemorrhoids) and a history of psychological/psychiatric conditions (based on self-report) or presently increased scores on the Hospital Anxiety and Depression Scale (HADS) (Herrmann-Lingen, Buss, & Snaith, 2005). Frequency and severity of gastrointestinal complaints suggestive of any functional or organic gastrointestinal condition were assessed with a standardized in-house questionnaire (Schmid et al., 2013) and personal interview. Briefly, the questionnaire assessed frequency and severity of gastrointestinal symptoms including diarrhoea, constipation, vomiting, nausea, lower abdominal pain, upper abdominal pain, heart burn, postprandial fullness, bloating, loss of appetite during the preceding month on a Likert-type rating scale (0 = experience never, 1 = experience once or twice per month, 2 = experience once or twice per week, to 3 = experience more than twice per week). Sum scores ≥ 10 were exclusionary.

To minimize (and standardize) putative anticipatory stress effects induced by the rectal distension procedure and/or the scanner environment, we included only subjects who were experienced with respect to both settings. However, none had previously participated in any kind of fear conditioning study. Only women on oral contraceptives were included. Pregnancy was routinely excluded by commercially available urinary test on the day of the study. The study protocol was approved by the local Ethics Committee (University Hospital Essen, Germany). All participants gave written informed consent and received 150 Euro for their participation.

2.2. Study design

The study design and conditioning protocol were previously described in detail (Kattoor et al., 2013). Briefly, rectal perceptual and pain thresholds were initially determined outside the scanner using established methodology (Benson et al., 2012; Elsenbruch et al., 2010, 2012; Schmid et al., 2013) (see below), followed by a structural MRI. Subsequently, event-related fMRI was used to measure neural activation during the anticipation and delivery of visceral stimuli in three consecutive scanning sessions, i.e., acquisition, extinction, reinstatement (for details, see section conditioning protocol). In all sessions, visual stimuli (CS^+ or CS^-) were presented. As unconditioned stimuli (US), painful rectal distensions at pressures 2 mmHg below the individual pain threshold (see below) were employed. At the conclusion of each session, subjects rated CS-pleasantness and unpleasantness, perceived CS-US contingency and present-state tension. Note that due to irregular availability of the scanner, the time of day was not standardized for these experiments, however, scanning times did not systematically differ between male and female participants.

2.3. Conditioning protocol

In the acquisition phase, painful rectal distensions (US) were paired with a predictive visual cue CS^+ while a second visual stimulus (CS^-) was presented without US (differential conditioning). A total of 32 CSs were presented (16 CS^+ ; 16 CS^-) in pseudo-randomized order with a 75% reinforcement schedule. The onset of the US presentation varied randomly between 7.2 s and 12s after CS^+ onset, and both stimuli were co-terminated (i.e., delay conditioning). In the extinction phase, only CSs (12 CS^+ ; 12 CS^-) with identical duration and order as in the acquisition phase were presented without US. In the reinstatement phase, one single unpaired US was delivered during the initial off-phase. Subsequently, only CSs (6 CS^+ ; 6 CS^-), were presented without US. Inter-trial intervals (ITI) were 20 s.

2.4. Online ratings

All stimuli and online rating scales were presented using commercially available stimulus delivery and experimental control software (Presentation[®], Neurobehavioral Systems, Albany, CA, USA) and were accomplished using an MRI-compatible hand-held fiber optic response system (LUMItouch[™], Photon Control Inc., Burnaby, BC, Canada). Subjects rated perceived pleasantness/unpleasantness of CS^+ and CS^- , and present-state tension prior to each session, as well as perceived pleasantness/unpleasantness of CS^+ and CS^- , perceived CS-US contingency, present-state tension, and distension-induced pain after each session on visual analogue scales (VAS). For analysis, all responses were quantified in mm (or % for contingency) from “0” to “100”, except for the combined pleasantness/unpleasantness scale which was quantified from minus 100 mm to plus 100 mm (with 0 mm indicating “neutral”).

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