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When gut feelings teach the brain to fear pain: Context-dependent activation of the central fear network in a novel interoceptive conditioning paradigm

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ABSTRACT

The relevance of contextual factors in shaping neural mechanisms underlying visceral pain-related fear learning remains elusive. However, benign interoceptive sensations, which shape patients' clinical reality, may context-dependently become conditioned predictors of impending visceral pain. In a novel context-dependent interoceptive conditioning paradigm, we elucidated the putative role of the central fear network in the acquisition and extinction of pain-related fear induced by interoceptive cues and pain-predictive contexts.

In this fMRI study involving rectal distensions as a clinically-relevant model of visceroception, $N = 27$ healthy men and women underwent differential conditioning. During acquisition training, visceral sensations of low intensity as conditioned stimuli (CS) predicted visceral pain as unconditioned stimulus (US) in one context (Con^+), or safety from pain in another context (Con^-). During extinction training, interoceptive CS remained unpaired in both contexts, which were operationalized as images of different rooms presented in the MRI scanner.

Successful contextual conditioning was supported by increased negative valence of Con^+ compared to Con^- after acquisition training, which resolved after extinction training. Although interoceptive CS were perceived as comparatively pleasant, they induced significantly greater neural activation of the amygdala, ventromedial PFC, and hippocampus when presented in Con^+, while contexts alone did not elicit differential responses. During extinction training, a shift from CS to context differentiation was observed, with enhanced responses in the amygdala, ventromedial, and ventrolateral PFC to Con^+ relative to Con^-, whereas no CS-induced differential activation emerged.

Context-dependent interoceptive conditioning can turn benign interoceptive cues into predictors of visceral pain that recruit key regions of the fear network. This first evidence expands knowledge about learning and memory mechanisms underlying interoceptive hypervigilance and maladaptive avoidance behavior, with implications for disorders of the gut-brain axis.

1. Introduction

As a translational model in cognitive and affective neurosciences, classical fear conditioning has contributed greatly to elucidating neural mechanisms underlying emotional learning and memory processes relevant to anxiety, trauma, and stress-related disorders (Duits et al., 2015; Pittig et al., 2018). Fear learning and extinction engage a widespread yet functionally connected group of brain regions associated with fear expression and regulation, including the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus, together with the insula and anterior cingulate cortex (ACC) (Fullana et al., 2018, 2016; Sehlmeyer et al., 2009). This central fear network is not only involved in the acquisition and extinction of conditioned fear in experimental settings in healthy individuals. It also shows altered activation patterns during symptom provocation in patients with anxiety disorders, and has been linked to effects of treatments built on principles of extinction learning, especially exposure therapy (Holzschneider and Mulert, 2011).

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Human fear conditioning has been expanded both conceptually and experimentally to incorporate pain as an intriguing condition clinically overlapping with anxiety and stress-related disorders (Velly and Mohit, 2018). Building on the unequivocal biological and clinical significance of pain, the role of conditioned pain-related fear is increasingly recognized in the development and treatment of chronic pain (Vlaeyen, 2015). Unraveling brain correlates of pain-related fear and extinction learning appears highly relevant and might be particularly interesting in the context of interoceptive visceral pain arising from the gastrointestinal (GI) tract. Visceral pain is of great clinical significance (Creed, 2019), induces high levels of fear (Dunckley et al., 2005; Koenen et al., 2017), and engages partially distinct neural networks when compared to exteroceptive, somatic pain (Dunckley et al., 2005; Koenen et al., 2017; Van Oudenhove et al., 2020). Recent findings comparing conditioning with visceral and somatic pain stimuli lend further support for unique behavioral and neural signatures of pain-related learning in the visceral domain (Benson et al., 2019; Koenen et al., 2018). Applying rectal distension-induced visceral pain as unconditioned stimuli (US) and visual cues as conditioned stimuli (CS), we previously elucidated behavioral and neural correlates of visceral pain-related fear learning and memory processes in healthy humans (Gramsch et al., 2014; Icenhour et al., 2015a, 2017; Kattoor et al., 2013; Labrenz et al., 2016, 2015) and in patients with chronic visceral pain (Icenhour et al., 2015b). While these findings widely support a role of the fear network also in visceral pain-related fear and extinction learning, existing paradigms have thus far not captured crucial aspects of patients' clinical reality, namely fear of interoceptive visceral sensations as predictors of pain and the role of contextual factors in modulating the formation of interoceptive cue-pain associations. Specifically, and of exceptional relevance to interoceptive hypervigilance and visceral pain, benign interoceptive GI signals frequently experienced also by healthy individuals conceivably induce fear if they become predictors of impending pain. Furthermore, rather than of isolated external cues, patients commonly experience fear of complex situations and environments where these bodily symptoms are experienced as particularly threatening. The concept of interoceptive learning has previously been introduced (De Peuter et al., 2011), mainly in experimental models of panic disorder (Benke et al., 2018; De Cort et al., 2017; Pappens et al., 2015). Within this framework, interoceptive CS naturally co-occurring with pain are expected to readily induce associative learning with „homoreflexive conditioning" involving CS and US from the same physiological system as one of the most powerful forms of classical conditioning (De Peuter et al., 2011). First evidence from research into gut-brain communication demonstrated the feasibility of visceral esophageal sensations as interoceptive predictors of either non-visceral (Zaman et al., 2016) or visceral US (Ceunen et al., 2016) to initiate associative learning processes, supporting the notion that innocuous gut signals may "teach" the brain to fear. However, little is known regarding interoceptive aversive learning with sensations from the lower GI tract and its modulation by contextual information, thus, *when* to fear, and the respective neural underpinnings particularly involving key regions of the central fear network remain elusive.

In this proof-of-concept fMRI study in healthy volunteers, we therefore implemented a novel context-dependent interoceptive conditioning paradigm with clinically-relevant visceral stimuli to elucidate the neural circuitry underlying the acquisition and extinction of contextually-modulated fear of interoceptive cues. We assessed whether benign interoceptive sensations may context-dependently turn into conditioned predictors of interoceptive pain. By pairing harmless visceral stimuli as CS with visceral pain as US in specific contexts, we tested in a ROI-based approach whether CS experienced in a threat-predictive context would induce an enhanced recruitment of the central fear network. Changes in valence of CS and/or contexts and contingency awareness were assessed as behavioral indicators of context-dependent interoceptive learning. Based on evidence suggesting fear extinction to be particularly context-dependent (Bouton, 2004), involving hippocampus and engaging prefrontal circuits relevant to emotion regulation (Milad and Quirk, 2012; Sotres-Bayon et al., 2006), we further hypothesized these regions to be differentially involved in context-dependent interoceptive extinction.

2. Materials and methods

2.1. Participants

Together, 27 healthy participants (12 women, 15 men) were recruited by local advertisement and included in this fMRI study. The recruitment procedure consisted of a structured telephone interview to screen participants for the following study-related exclusion criteria: age <18 or >45 years, body mass index (BMI) <18 or >30 kg/m^2, MRI-related criteria (e.g., claustrophobia, ferromagnetic implants), any known medical condition including gastrointestinal, neurological, psychiatric, or endocrinological disease, and frequent medication use (except hormonal contraceptives, thyroid medications, or occasional use of over-the-counter allergy or pain medications). If eligible, a personal interview followed during which standardized study-related information was provided, and informed written consent was acquired. Participants were informed that the study goal was to investigate the neural processing of interoceptive visceral stimuli of different intensities and of the context in which these are experienced. No information regarding experimental phases, contingency changes or relations between contexts and visceral stimulation was disclosed. The German version of the Hospital Anxiety and Depression Scale (HADS; Snaith, 2003) was implemented as a screening tool for current symptoms of anxiety or depression and for sample characterization regarding psychological complaints. In addition, the screening scale of the Trier Inventory of Chronic Stress (TICS; Schulz et al., 2004) served to characterize participants with respect to chronic stress load.

Upon arrival, before, and at the conclusion of the experiment on the study day, state anxiety was further assessed using the state version of the State Trait Anxiety Inventory (STAI; Laux et al., 1981) to characterize participants with respect to transient emotional states. All participants were right-handed, as confirmed with a validated questionnaire on motor asymmetries (Oldfield, 1971). Only women using hormonal contraception were included in the study to reduce a putative confounding effect of fluctuations in sex steroid hormones across the menstrual cycle in female participants. This approach was chosen based on previous findings documenting effects of gonadal hormone concentrations and menstrual cycle phase on both, the perception of visceral symptoms (Mulak et al., 2014) and emotional learning, including involved neural mechanisms (Hwang et al., 2015; Merz et al., 2012). Pregnancy was ruled out with a commercially available urinary test on the study day. In addition, a physical examination was conducted to exclude perianal tissue damage (i.e., fissures or painful hemorrhoids) which could interfere with the experimental procedures. Symptoms suggestive of functional or organic gastrointestinal conditions were excluded using a standardized questionnaire (Lacourt et al., 2014). Structural brain abnormalities were excluded based on structural MRI. The study protocol was approved by the local ethics committee (protocol number 16–7226-BO) and followed the provisions of the Declaration of Helsinki. All participants gave informed written consent and received a financial compensation for their participation.

2.2. Interoceptive stimuli

As clinically-relevant interoceptive visceral conditioned (CS) and unconditioned stimuli (US), pressure-controlled rectal distensions were applied using a barostat system (modified ISOBAR 3 device, G & J Electronics, ON, Canada). This well-established experimental model allows the controlled application of graded distensions of different perceptual intensities, which approximate interoceptive sensations patients with visceral pain conditions but also healthy men and women commonly experience (Elsenbruch and Labrenz, 2018; Keszthelyi et al., 2012). Building

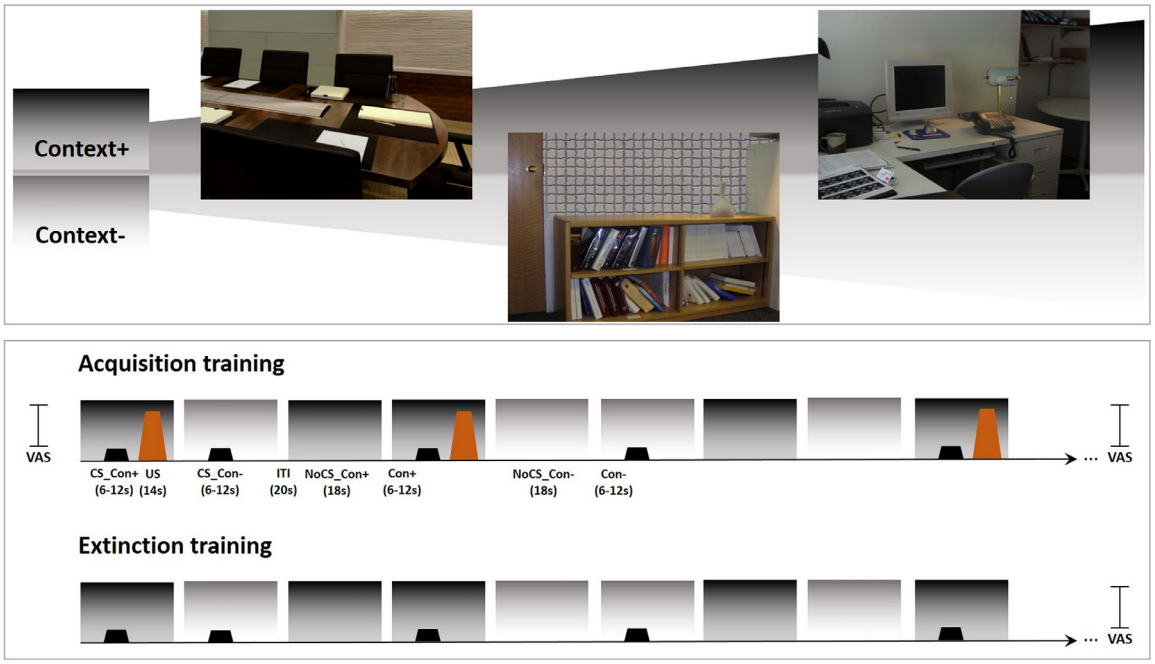

Fig. 1. Experimental protocol. Images of different rooms presented in the scanner (upper row), served as either context^{+} (Con^{+}) or context^{-} (Con^{-}) in this context-dependent interoceptive conditioning paradigm. During acquisition training, interoceptive visceral cues were followed by a visceral pain stimulus in context^{+} (CS_Con^{+}) and remained unpaired in context^{-} (CS_Con^{-}) during CS trials. The same number of NoCS trials consisted of context^{+} (NoCS_Con^{+}) and context^{-} (NoCS_Con^{-}) presentations without interoceptive CS or US application. During extinction training, contexts were presented with interoceptive CS during CS trials and in absence of interoceptive CS during NoCS trials and no US were delivered. At baseline and at the conclusion of experimental phases, visual analog scale (VAS) ratings to assess emotional, perceptual, and cognitive measures were accomplished.

on our prior experience in the application of rectal distensions as interoceptive US in conditioning studies accomplished in healthy individuals (Gramsch et al., 2014; Icenhour et al., 2015a, 2017; Kattoor et al., 2013; Labrenz et al., 2016) and in patients with chronic visceral pain (Icenhour et al., 2015b), we herein for the first time also applied interoceptive visceral CS.

In order to identify individualized stimulus intensities for CS and US presentations during the subsequent experimental procedures, visceral sensory and pain thresholds were initially assessed prior to scanning. To do so, double-random staircase distensions with random pressure increments of 2–8 mmHg and 30 second durations were delivered, as previously accomplished (Icenhour et al., 2015a, 2019; Labrenz et al., 2016). Participants were prompted to rate each distension on a Likert-type scale with the labels 1 = no perception, 2 = doubtful perception, 3 = sure perception, 4 = little discomfort, 5 = severe discomfort, still tolerable distension and 6 = pain, not tolerable distension. Sensory thresholds were defined as the pressure when ratings changed from 2 to 3 and pain thresholds were determined as a change from 5 to 6. Based on established methodology for calibrating stimulus intensities regarding their perceptual characteristics (Icenhour et al., 2017; Koenen et al., 2018, 2017), these individual thresholds were used as anchors for the identification of intensities defined as “perceivable but neither uncomfortable, nor painful” for CS and as “moderately painful, but still tolerable” for US, respectively. Specifically, participants were asked to rate the intensity of a pressure above individual sensory threshold on a 0 – 100 mm visual analogue scale (VAS) with endpoints labelled “no perception” and “very painful” and pressures were adjusted, if necessary, in steps of 1 mmHg to identify a pressure corresponding to a rating between 20 and 30, which was chosen as CS. An equal procedure was conducted using a pressure below individual pain threshold as an anchor to define a US intensity corresponding to VAS ratings between 60 and 80 for repeated applications during the subsequent experiment.

For safety reasons, a maximal distension pressure of 50 mmHg was set. Unlike exteroceptive sensations such as heat pain, repeated application of rectal distensions does not appear to show habituation effects in healthy individuals (Koenen et al., 2018, 2017), irrespective of their intensity (Icenhour et al., 2017). Given that stable perceptual characteristics of CS and US are integral to this paradigm, CS and US were further presented and rated following structural MRI in the scanner immediately before the beginning of the experimental procedures to acquire a respective baseline intensity (see below).

2.3. Experimental design

All measurements with an overall duration of approximately 90 min were performed at the MRI suite of the University Hospital Essen, and conducted between 16:00 and 19:00 h to minimize possible circadian rhythm effects. Following thresholding, calibration, and a structural MRI, BOLD responses were acquired during consecutive experimental acquisition and extinction phases, as illustrated in Fig. 1.

Three graphical images of rooms adapted from previous work addressing context effects on fear and extinction learning in a scanner environment (Hermann et al., 2016; Milad et al., 2007) were used as contexts herein. Randomized across participants, two of these images were allocated to serve as a pain- or safety-predictive context, projected onto a mirror mounted on the head coil, during the experiment. During the first time interval of each trial, contexts (Con^{+} / Con^{-}) were presented alone with a variable duration between 6 and 12 s. In CS trials, an interoceptive visceral CS was additionally applied with an identical individualized intensity in either context (CS_Con^{+} / CS_Con^{-}) and a duration between 6 and 12 s. In each trial, Con plus CS_ Con presentations together equaled 18 s. During acquisition training, this visceral CS was directly followed by a visceral pain stimulus as US (duration 14 s) in Con^{+}, whereas no US was applied in Con^{-}. The paradigm further included trials in which solely contexts were presented but no intero-

ceptive CS and no US were delivered, allowing a distinct assessment of neural responses to the absence of expected interoceptive cues in either context (NoCS_Con$^+$ / NoCS_Con$^-$). In these NoCS trials, contexts were presented for 18 s, equivalent to the duration of the first time interval of context presentation alone (Con) plus the second time interval of context with CS presentations (CS_Con) in CS trials. The total number of trials for the acquisition phase was 32 (i.e., 8 trials of each context presentation in the CS and NoCS condition, respectively) presented in pseudorandomized order and a reinforcement rate of 50% was applied (i.e., 100% reinforcement in CS trials). Extinction training consisted of the same conditions and number of trials, but interoceptive CS were never followed by US. Intertrial intervals were 20 s, during which a black screen with a light gray frame was presented. Varying delays between context, CS, and US presentations were utilized to induce uncertainty and to generate more robust conditioned responses (Sehlmeyer et al., 2009). To improve temporal resolution, a variable jittering image acquisition technique was used (Amaro and Barker, 2006).

2.4. Behavioral measures of pain-related learning and extinction

As behavioral measures of pain-related context and cue conditioning and extinction, online VAS valence ratings were accomplished at baseline and at the conclusion of each experimental phase using an MR-compatible hand-held response device. Contingency awareness was evaluated following acquisition and extinction training by presenting Con$^+$ and Con$^-$ and prompting participants to respond to the question "How often did you experience a pain stimulation in this context?" on VAS with endpoints labeled "never" (0) and "always" (100). To assess context valence, participants were presented each context and responded to the question "How do you perceive this context?" on a VAS with neutral indicated in the middle of the scale (0) and endpoints labeled "very pleasant" (−100) and "very unpleasant" (100). For CS valence, an interoceptive CS was applied without displaying a context at baseline and in Con$^+$ and Con$^-$ after acquisition and extinction training, respectively, and participants responded to the question "How do you perceive this stimulus?" on the same VAS as used for context valence. At baseline and at the conclusion of acquisition training, participants further rated US valence on an identical VAS with no context presentation. In addition, CS and US intensity were determined using the same VAS as during the calibration procedure to confirm successful titration of stimulus intensities and to test for possible changes across experimental phases.

2.5. Statistical analyses of behavioral data

Statistical analyses of behavioral data were computed with IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY, USA). Initially, normal distribution of behavioral outcomes was confirmed using Kolmogorov–Smirnov tests and parametric testing was subsequently applied. For ratings of context-US contingencies, repeated measures analysis of variance (RM-ANOVA) with the within-subject factors *time point* (acquisition training, extinction training) and *stimulus type* (Con$^+$, Con$^-$) were calculated. RM-ANOVA were further conducted for context valence and for CS valence and intensity, including the within-subject factors *time point* (baseline, acquisition training, extinction training) and *stimulus type* (Con$^+$, Con$^-$ or CS_Con$^+$, CS_Con$^-$, respectively). US valence and intensity were analyzed using paired t-tests. ANOVA results are reported with Greenhouse-Geisser correction and results of post hoc paired t-tests were Bonferroni-corrected for multiple comparisons. State anxiety across the experimental phases was analyzed using RM-ANOVA with the within-subject factor *time point* (upon arrival, before experiment, after experiment). The alpha level for accepting statistical significance was set at $p < .05$. All data are shown as mean ± standard error of the mean (SEM), unless indicated otherwise and effect sizes are provided as η_p^2 or Cohen's *d,* respectively.

2.6. Brain imaging and analyses

Structural and functional MRI data were acquired on a 3 Tesla whole body scanner equipped with a 32-channel head coil (Skyra, Siemens Healthcare, Erlangen, Germany). For structural images, a 3D-MPRage T_1-weighted sequence (TR 1770 ms, TE 3.24 ms, flip angle 8°, FOV 256 × 256 mm^2, 224 slices, slice-thickness 1.0 mm, voxel size 1.0 × 1.0 × 1.0 mm^3, matrix 256 × 256 mm^2) was acquired. BOLD contrast images were recorded using an EPI sequence with the following parameters: TR 2400 ms, TE 28.0 ms, flip angle 90°, FOV 240 × 240 mm^2, matrix 104 × 104 mm^2 and GRAPPA $r = 2$ and 38 transversal slices angulated in direction of the corpus callosum with a thickness of 3 mm, a voxel-size of 2.3 × 2.3 × 3 mm^3 and a 0.6 mm slice gap effectively covering the whole brain.

Data preprocessing and analyses were accomplished using SPM12 (Wellcome Trust centre for Neuroimaging, UCL, London, UK) implemented in Matlab R2018a (Mathworks Inc., Sherborn, MA, USA). Using the CAT 12 toolbox (Computational Anatomy Toolbox 12; http://www.neuro.uni-jena.de/cat/) implemented in SPM12, structural T_1-weighted images with the origin set to the anterior commissure were spatially registered to the MNI template and segmented into gray matter, white matter, and cerebrospinal fluid in preparation for the coregistration and normalization of functional images. Bias correction was performed to remove intensity non-uniformities. Functional images were motion corrected and realignment parameters describing the rigid body transformation between each image and the mean image used as a reference image were estimated. Images were coregistered to the skull-stripped individual T1-weighted image used as a reference image, normalized to MNI space using a standardized template implemented in SPM12 and spatially smoothed with an isotropic Gaussian kernel of 6 mm. A temporal high-pass filter of 128 s was used to correct for low frequency drifts in the data. Serial autocorrelations were accounted for by means of an autoregressive model 1st order correction.

For statistical 1st level analyses, a GLM was applied to the EPI images with regressors modeled based on a stick function convolved with the canonical HRF (event-related design). The 1st level model included acquisition and extinction training as separate sessions with the following respective regressors: context$^+$ (Con$^+$), context$^-$ (Con$^-$) with 16 trials per phase, i.e., involving the first time interval with context presentations alone in CS and in NoCS trials, CS in context$^+$ (CS_Con$^+$), CS in context$^-$ (CS_Con$^-$) and, for NoCS trials, absence of CS in context$^+$ (NoCS_Con$^+$) and absence of CS in context$^-$ (NoCS_Con$^-$) with 8 trials per phase, respectively. For acquisition training, the regressor US (8 trials) was further entered. In addition, realignment parameters were included as nuisance regressors for motion correction. Each regressor was modeled with the respective stimulus onset and a duration of 0 s. For an estimation of responses to the absence of expected interoceptive CS during NoCS trials, variable onsets between 6 and 12 s after the initial context presentation were defined. The respective onset corresponded to the length of context presentation during the first time interval, i.e., until CS onset, of the preceding CS trial in the same context.

To assess differential BOLD responses to contexts, CS, and the omission of CS in NoCS trials during acquisition and extinction training, the following 1st level contrasts and the respective reverse contrasts were computed for each phase and entered into 2nd level group analyses using paired t-tests: [Con$^+$ > Con$^-$], [CS_Con$^+$ > CS_Con$^-$], [NoCS_Con$^+$ > NoCS_Con$^-$]. In addition to analyses addressing the full phase of acquisition and extinction training, exploratory analyses comparing early and late phases (i.e., first half vs. second half of the respective phase) were conducted to assessed changes over time ([Con$^+$ > Con$^-$ early >> Con$^+$ > Con$^-$ late], [CS_Con$^+$ > CS_Con$^-$ early >> CS_Con$^+$ > CS_Con$^-$ late], [NoCS_Con$^+$ > NoCS_Con$^-$ early >> NoCS_Con$^+$ > NoCS_Con$^-$ late] and vice versa, for acquisition and extinction training, respectively). Finally, comparisons of differential activation patterns during acquisition and extinction were explored ([Con$^+$ > Con$^-$ Acquisition >> Con$^+$ > Con$^-$ *Extinction*], [CS_Con$^+$ > CS_Con$^-$ Acquisition >>

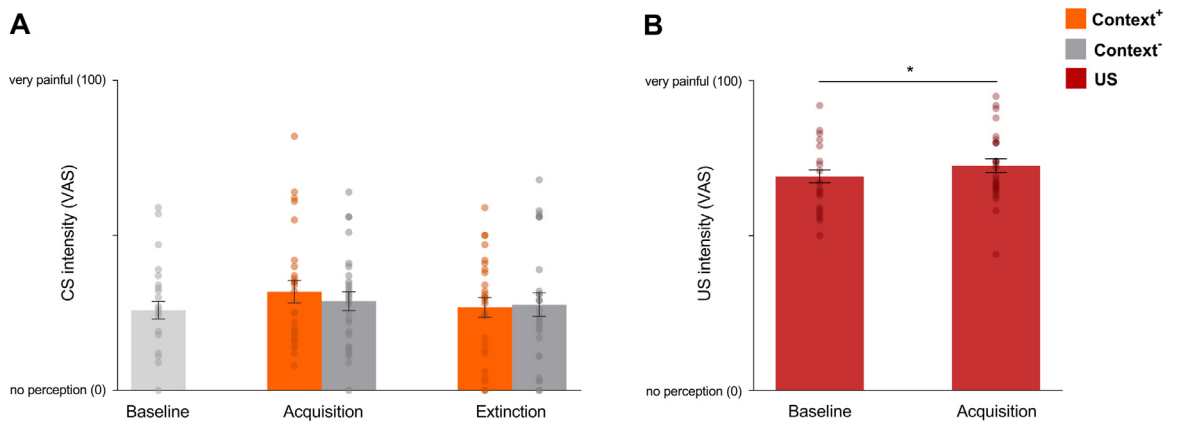

Fig. 2. Ratings of perceived CS and US intensity. Results of visual analog scale (VAS) ratings of (A) CS intensity assessed at baseline and following acquisition and extinction training, and (B) US intensity evaluated at baseline and at the conclusion of acquisition training. Data are given as mean ± SEM. * $p < .05$.

CS_Con$^+$ > CS_Con$^-$ Extinction], [NoCS_Con$^+$ > NoCS_Con$^-$ Acquisition >> NoCS_Con$^+$ > NoCS_Con$^-$ Extinction] and vice versa). On the 2nd level, mask-based ROI analyses with small volume correction were performed using vmPFC together with ventrolateral, and dorsolateral PFC (vlPFC, dlPFC), amygdala, hippocampus, ACC, and insula as a priori defined ROI. Choice of ROI was based on previous findings on cue and context conditioning and extinction of fear, including prefrontal nodes crucially involved in emotion regulation (Fullana et al., 2018, 2016; Kalisch et al., 2006; Milad et al., 2007; Milad and Quirk, 2012; Sotres-Bayon et al., 2006), and our own work on visceral pain-related learning and memory (Icenhour et al., 2015a, 2017; Koenen et al., 2018; Labrenz et al., 2016). ROI analyses were carried out using anatomical templates as provided by the WFU Pick Atlas toolbox (Version 2.5.2; (Maldjian et al., 2003)) integrated into the SPM software environment. Contrast estimates were extracted to visualize the direction of observed effects and were entered into Pearson's correlation analyses to explore associations of neural responses with behavioral measures. All results from fMRI analyses are given as MNI coordinates and voxel-level results ($k_E \geq 3$) with familywise error (FWE) correction for multiple comparisons set at $p_{FWE} < .05$ are reported for all ROI analyses. For completeness, exploratory whole brain analyses of US-induced neural responses are further reported, thresholded at $p < .001$ uncorrected ($k_E \geq 10$).

3. Results

3.1. Sample characterization

Participants (44.44% women; mean age 25.74 ± 0.95 years; mean BMI 23.56 ± 0.59 kg/m^2) presented with overall few psychological symptoms (HADS anxiety: 3.81 ± 0.49; HADS depression: 2.22 ± 0.38) and reported low chronic stress (14.89 ± 1.62), consistent with stringent exclusion criteria. Mean rectal sensory thresholds were determined as 15.93 ± 0.99 mmHg, mean rectal pain thresholds as 34.96 ± 1.97 mmHg, in accordance with previous findings on visceral pain sensitivity in young healthy participants (Icenhour et al., 2019). Analyses of state anxiety across the experiment showed a main effect of *time point* ($F_{(2,52)} = 3.73$; $p = .044$; $\eta_p^2 = 0.139$), which resulted from a decrease in state anxiety across the experiment (data not shown).

3.2. Ratings of CS and US intensity

Statistical details of CS and US intensity ratings are provided in Table 1A. Analyses of intensity ratings at baseline confirmed successful calibration of CS (25.85 ± 2.85) and US (69.15 ± 2.08) intensities to target ranges of 20–30 and 60–80 on 0–100 mm VAS, respectively, and demonstrated a clear differentiation between the two interoceptive stimulus intensities (Table 1A; Fig. 2). RM-ANOVA assessing putative changes in intensity perception of CS revealed no significant findings across the experimental phases (Table 1A; Fig. 2A). Regarding US ratings, *t*-test revealed a subtle increase in perceived pain intensity assessed after acquisition training relative to baseline (Table 1A; Fig. 2B). These findings document a substantial differentiation of interoceptive CS and US intensities, with a small, yet significant increase for visceral US after repeated presentations during acquisition, which, however, stayed well within the predefined range of VAS 60–80, and stable intensities of interoceptive CS. These data widely confirmed earlier observations from trial-by-trial ratings of both painful, and non-painful experimental visceral stimulation (Icenhour et al., 2017; Koenen et al., 2018, 2017).

3.3. Behavioral correlates of interoceptive contextual conditioning and extinction

Contingency awareness regarding context-US pairings was assessed following acquisition and extinction training. Successful differential contextual conditioning was supported by a main effect of *time point* and *stimulus type*, as well as a significant *time point* x *stimulus type* interaction. Post hoc tests revealed significantly higher VAS contingency ratings for Con$^+$ (62.67 ± 3.37) relative to Con$^-$ (39.26 ± 4.57) following acquisition training (Table 1B; Fig. 3A). Ratings of Con$^+$-US contingencies were decreased after extinction training relative to post acquisition training, whereas no change across phases was detectable for Con$^-$ contingencies, resulting in virtually identical Con$^+$ (35.48 ± 4.06) and Con$^-$ (39.22 ± 5.48) contingency ratings at the conclusion of extinction training (Table 1B; Fig. 3A). Contingency data further indicated that while Con$^+$-US contingencies for the acquisition (*de facto* 50% considering CS and NoCS trials) were widely accurate, contingencies for Con$^-$ across experimental phases and for Con$^+$ after extinction (*de facto* 0%) were overestimated.

As emotional components of pain-related learning and extinction, valence of contexts, CS, and US across experimental phases were analyzed. RM-ANOVA addressing context valence as a marker of pain-related fear revealed a main effect of *time point* and an interaction between *time point* and *stimulus type*, while no significant main effect of *stimulus type* emerged (Table 1C; Fig. 3B). The interaction effect was attributable to a significant increase in negative valence for Con$^+$ but not Con$^-$ from baseline to acquisition. This resulted in a differentiation following acquisition training, which, however, was not significant after Bonferroni correction. Compared to ratings after acquisition training, the observed negative Con$^+$ valence was resolved after extinction training, while no difference between these time points was observed for Con$^-$. Context valence ratings were comparable at the conclusion of extinction training. See Table 1C and Fig. 3B for statistical details and a visualization of results from post hoc t-tests.

Table 1
Context-, CS- and US-related behavioral markers of context-dependent interoceptive acquisition and extinction training.

	Measure	Effect	df	F/t	*p*	η_p^2/d
A	CS vs US intensity	*CS vs US baseline*	26	12.37	**<.001**	2.379
	CS intensity	*time point*	2,52	1.25	.292	.046
		stimulus type	1,26	0.30	.590	.011
		time point x stimulus type	2,52	0.68	.471	.025
	US intensity	*US baseline vs acquisition*	26	2.38	**.025**	0.458
B	Context contingency	*time point*	1,26	13.83	**.001**	.347
		stimulus type	1,26	4.57	**.042**	.149
		time point x stimulus type	1,26	12.96	**.001**	.333
	Post hoc	*Con⁺ vs Con⁻ acquisition*	26	3.68	**.001**	0.708
		Con⁺ acquisition vs extinction	26	5.95	**.001**	1.145
		Con⁻ acquisition vs extinction	26	0.01	> .99	0.001
		Con⁺ vs Con⁻ extinction	26	0.68	.503	0.131
C	Context valence	*time point*	2,52	8.24	**.001**	.241
		stimulus type	1,26	1.33	.260	.049
		time point x stimulus type	2,52	3.81	**.036**	.128
	Post hoc	*Con⁺ vs Con⁻ acquisition*	26	2.07	.144	0.399
		Con⁺ baseline vs acquisition	26	2.88	**.023**	0.750
		Con⁻ baseline vs acquisition	26	2.20	.111	0.423
		Con⁺ acquisition vs extinction	26	2.59	**.047**	0.611
		Con⁻ acquisition vs extinction	26	0.98	.995	0.188
		Con⁺ vs Con⁻ extinction	26	0.65	> .99	0.125
D	CS valence	*time point*	2,52	0.77	.467	.029
		stimulus type	1,26	0.09	.766	.003
		time point x stimulus type	2,52	0.07	.905	.003
	US valence	*US baseline vs acquisition*	26	1.45	.160	0.290

Results of RM-ANOVA and paired t-tests addressing (A) CS and US intensity, (B) context-US contingencies, (C) context valence and (D) CS and US valence within and across experimental phases. For all analyses, exact *p* values are provided with Bonferroni correction for post hoc tests. Abbreviations: Con, context; CS, conditioned stimulus; US, unconditioned stimulus.

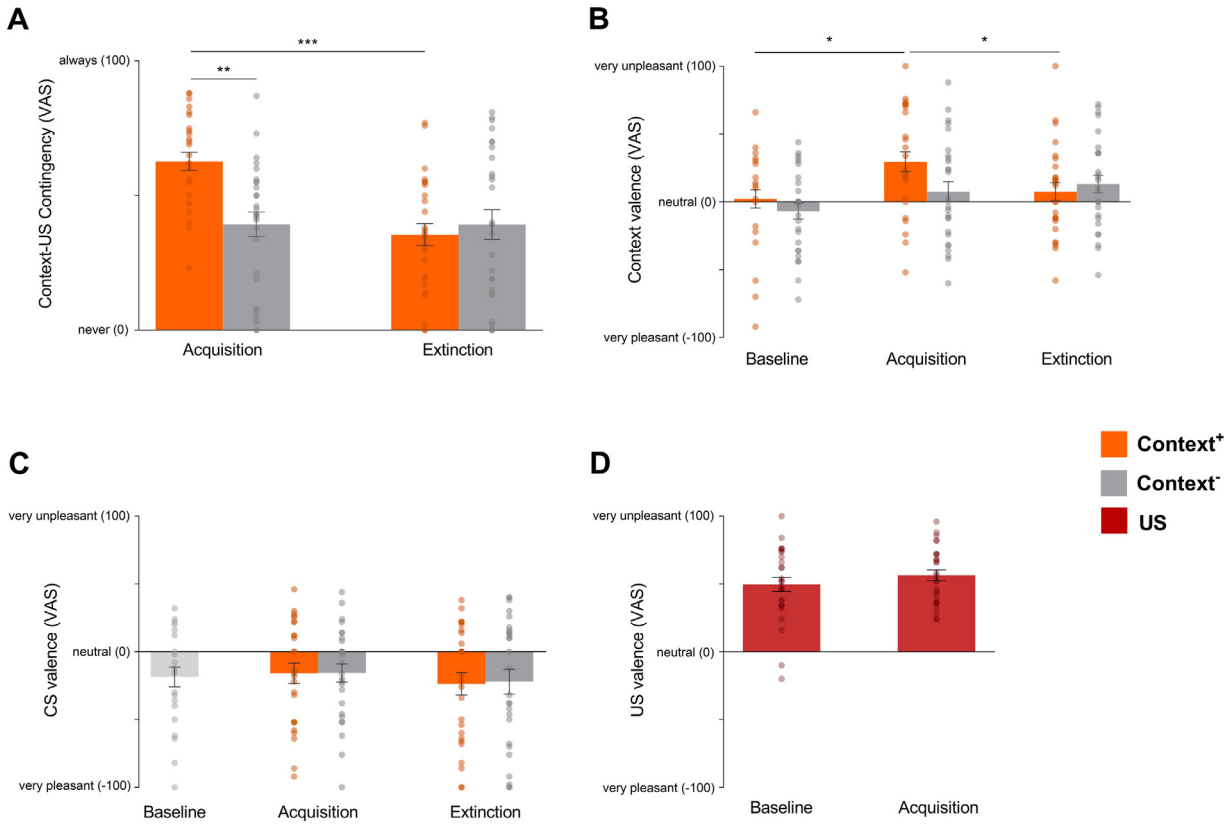

Fig. 3. Behavioral correlates of interoceptive context-dependent pain-related acquisition and extinction learning. Results of visual analog scale (VAS) ratings of (A) context-US contingency, as assessed following acquisition and extinction training, (B) context valence, (C) CS valence, evaluated at baseline and at the conclusion of each experimental phase, and (D) US valence at baseline and following acquisition training. Data are given as mean ± SEM. * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 2
Differential neural responses during acquisition of context-dependent interoceptive pain-related fear.

Contrast	ROI		Coordinates					
		H	x	y	z	t-value	P_{FWE}	k_E
$Con^+ > Con^-$	–	–	–	–	–	–	–	–
$Con^- > Con^+$	–	–	–	–	–	–	–	–
$CS\_Con^+ > CS\_Con^-$	Amygdala	R	28	4	−17	4.60	.011	52
	vmPFC	–	1	26	−13	4.75	.026	297
	vmPFC	–	−5	29	−17	4.38	.016	130
	Hippocampus	R	37	−12	−24	6.36	.001	196
	Hippocampus	L	−32	−27	−13	5.45	.007	331
$CS\_Con^- > CS\_Con^+$	–	–	–	–	–	–	–	–
$NoCS\_Con^+ > NoCS\_Con^-$	Amygdala	R	22	−7	−12	3.94	.044	11
	pdACC	–	4	−8	42	4.69	.023	180
$NoCS\_Con^- > NoCS\_Con^+$	–	–	–	–	–	–	–	–

Results of region of interest analyses regarding differential BOLD responses induced by contexts preceding visceral CS onset [$Con^+ > Con^-$], interoceptive CS [$CS\_Con^+ > CS\_Con^-$] and the absence of expected CS [$NoCS\_Con^+ > NoCS\_Con^-$] and the respective reverse contrasts during interoceptive context-dependent pain-related fear acquisition training. Results of voxel-based analyses are provided, and exact unilateral p values are given (all $p_{FWE} < .05$). H, hemisphere; k_E, cluster size; L, left; pdACC, posterior dorsal anterior cingulate cortex; R, right; ROI, region of interest; vmPFC, ventromedial prefrontal cortex.

Table 3
Differential neural responses during extinction of context-dependent interoceptive pain-related fear.

Contrast	ROI		Coordinates					
		H	x	y	z	t-value	P_{FWE}	k_E
$Con^+ > Con^-$	Amygdala	R	29	−3	−23	4.24	.016	42
	vlPFC	L	−33	21	−22	5.19	.015	126
	vlPFC	R	45	31	−1	5.69	.008	605
	vmPFC	–	−8	53	3	4.74	.033	50
$Con^- > Con^+$	–	–	–	–	–	–	–	–
$CS\_Con^+ > CS\_Con^-$	–	–	–	–	–	–	–	–
$CS\_Con^- > CS\_Con^+$	–	–	–	–	–	–	–	–
$NoCS\_Con^+ > NoCS\_Con^-$	sgACC / vmPFC	–	−2	11	−10	4.87	.004	39
$NoCS\_Con^- > NoCS\_Con^+$	–	–	–	–	–	–	–	–

Results of region of interest analyses regarding differential neural activation induced by contexts preceding visceral CS onset [$Con^+ > Con^-$], interoceptive CS [$CS\_Con^+ > CS^-$] and the absence of expected CS [$NoCS\_Con^+ > NoCS\_Con^-$] and the respective reverse contrasts during interoceptive context-dependent pain-related fear extinction training. Results of voxel-based analyses are provided, and exact unilateral p values are given (all $p_{FWE} < .05$). H, hemisphere; k_E, cluster size; L, left; R, right; ROI, region of interest; sgACC, subgenual anterior cingulate cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

ANOVA of CS valence revealed no significant effects (Table 1D; Fig. 3C), indicating similar evaluations of CS experienced in Con^+ and in Con^- with no learning-induced changes. Interestingly, while US were rated as comparably unpleasant at baseline (49.56 ± 5.28) and following repeated exposure (56.37 ± 4.06; Table 1D; Fig. 3D), CS were consistently perceived as rather pleasant stimuli across experimental phases.

3.4. Neural correlates of context-dependent interoceptive conditioning and extinction

Findings of differential BOLD responses to contexts, interoceptive CS, and, in NoCS trials, to phases of CS absence are summarized in Table 2 for acquisition training and in Table 3 for extinction training. During acquisition training, Con^+ alone did not induce differential neural activation relative to Con^-. Interoceptive CS applied in Con^+ led to enhanced neural responses in the amygdala, vmPFC, and bilateral hippocampus when compared to identical visceral CS in Con^- (Fig. 4). In addition, when expected CS remained absent in NoCS trials, enhanced differential activation of the amygdala and the posterior proportion of dorsal ACC (pdACC) in Con^+ compared to Con^- was observed (Fig. 5). No differential activation was detected in any respective reverse contrast and exploratory analyses comparing early vs. late acquisition revealed no significant findings for either contrast. Results of exploratory whole brain analyses regarding neural responses induced by visceral painful US during acquisition training showed a widespread network including somatosensory and prefrontal regions, thalamus, insula, and amygdala, as detailed in supplementary Table 1 and illustrated in supplementary Figure 1.

During extinction training, enhanced activation of vmPFC, bilateral vlPFC, and amygdala in response to Con^+ compared to Con^- was observed (Fig. 6A; Table 3), whereas no differentiation of CS was evident. A differential engagement of subgenual ACC / vmPFC was induced in the absence of CS in Con^+ relative to Con^- in NoCS trials (Fig. 6B; Table 3). The respective reverse contrasts did not yield significant findings and comparisons of early vs. late extinction did not reveal significant differential responses to contexts, CS, and NoCS.

3.5. Exploratory comparisons of neural activation during acquisition and extinction training

To assess putative changes in neural responses across experimental phases, exploratory analyses were conducted comparing differential neural activation during acquisition with those during extinction training. Analyses of context-induced differential responses [$Con^+ > Con^-$]

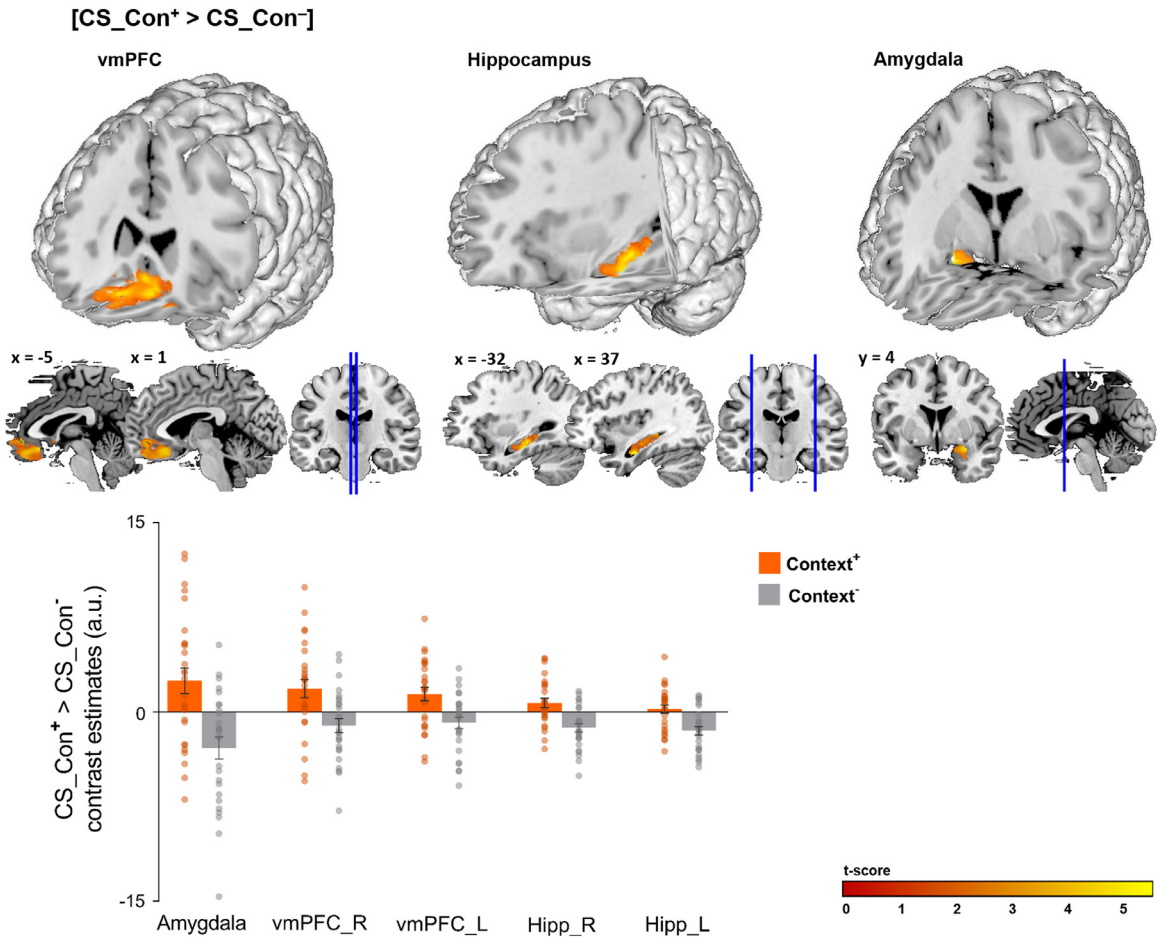

Fig. 4. Differential neural activation to interoceptive CS during pain-related fear acquisition training. Differential BOLD responses induced by interceptive CS [CS_Con$^+$ > CS_Con$^-$] during acquisition training. Activations were superimposed on a structural T_1-weighted MRI, thresholded at $p < .05$ uncorrected, and masks for relevant ROI were applied for visualization purposes; color bar indicates t-scores and contrast estimates are provided to indicate the direction of effects. For statistical details, see Table 2. Abbreviations: a. u., arbitrary units; Hipp, Hippocampus; L, left; R, right; vmPFC, ventromedial prefrontal cortex.

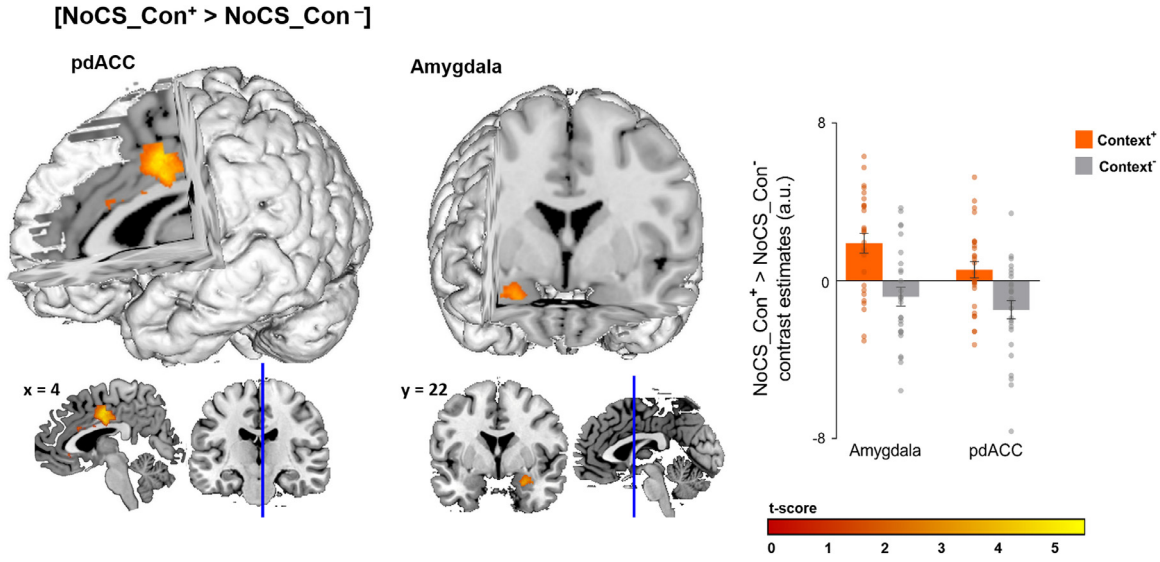

Fig. 5. Differential neural activation to the absence of expected CS during interoceptive pain-related fear acquisition training. Differential BOLD responses induced by the absence of expected CS [NoCS_Con$^+$ > NoCS_Con$^-$] during acquisition training. Activations were superimposed on a structural T_1-weighted MRI, thresholded at $p < .05$ uncorrected, and masks for relevant ROI were applied for visualization purposes; color bar indicates t-scores and contrast estimates are provided to indicate the direction of effects. For statistical details, see Table 2. Abbreviations: pdACC, posterior dorsal anterior cingulate cortex.

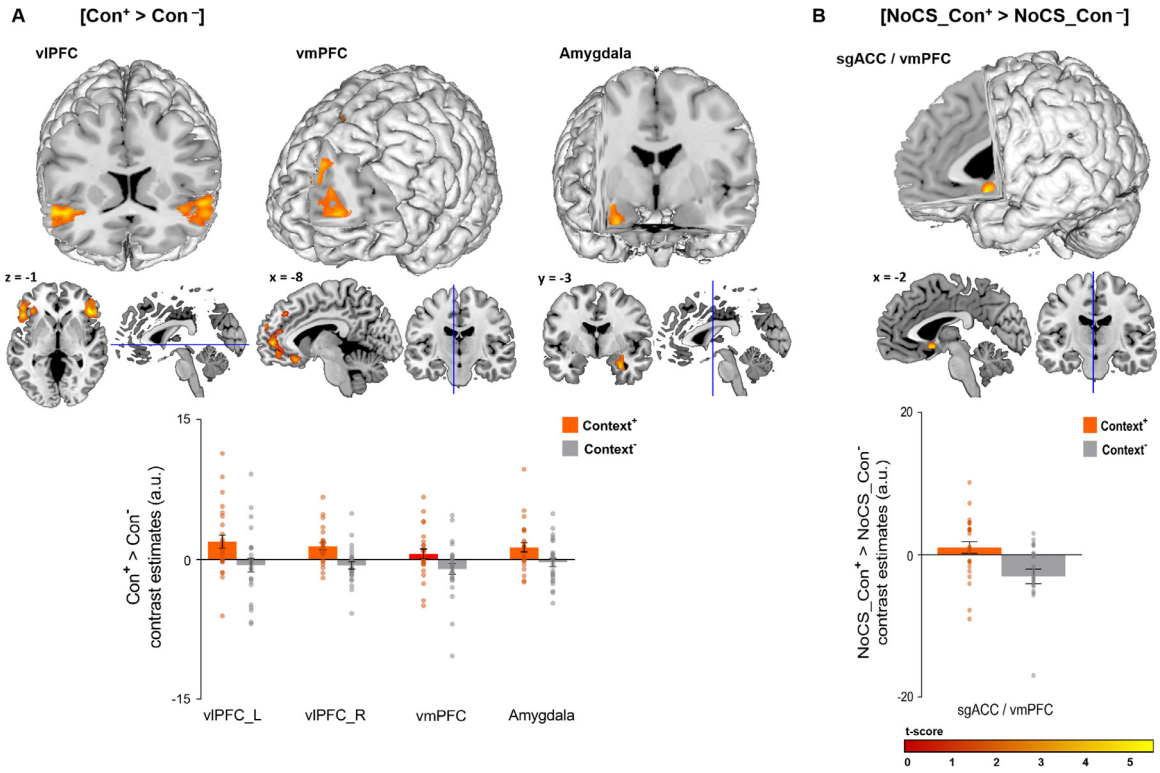

Fig. 6. Differential neural activation during interoceptive contextual pain-related extinction training. Differential BOLD responses induced by (A) contexts [Con^+ > Con^-] and (B) the absence of expected CS [$NoCS\_Con^+$ > $NoCS\_Con^-$] during extinction. Activations were superimposed on a structural T_1-weighted MRI, thresholded at $p < .05$ uncorrected, and masks for relevant ROI were applied for visualization purposes; color bar indicates t-scores and contrast estimates are provided to indicate the direction of effects. For statistical details, see Table 3. Abbreviations: A, anterior; L, left; P, posterior; R, right; sgACC, subgenual anterior cingulate cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

revealed a stronger involvement of vlPFC during acquisition relative to extinction ($x = -41$, $y = 11$, $z = 12$; $t = 4.36$; $p = .019$), while enhanced differential responses of parahippocampus were evident during extinction when compared to acquisition training ($x = -17$, $y = -16$, $z = -24$; $t = 4.03$; $p = .046$). For CS-induced neural responses [CS_Con^+ > CS_Con^-], enhanced involvement of pdACC ($x = -11$, $y = 8$, $z = 49$; $t = 4.37$; $p = .036$) and MCC ($x = -11$, $y = 19$, $z = 37$; $t = 4.76$; $p = .014$) was evident during acquisition compared to extinction, whereas CS during extinction did not appear to engage enhanced differential neural activation relative to acquisition. No differences emerged for differential NoCS-related responses across experimental phases.

3.6. Exploratory analyses of associations between neural responses and behavioral markers of context-dependent interoceptive conditioning and extinction

Significant results of exploratory correlational analyses of brain imaging and behavioral findings are provided in supplementary Table 2. Briefly, for acquisition, CS_Con^-- induced hippocampal responses showed a positive association with Con^+ contingency and were negatively correlated with CS valence ratings in both, Con^+ and Con^- following acquisition. Con^- contingency ratings were strongly ($p < .01$) negatively associated with pdACC activation to Con^+ in NoCS trials and contrast estimates extracted from pdACC correlated negatively with CS_Con^+ and CS_Con^- valence ratings. For extinction, context-induced BOLD responses of left vlPFC showed negative associations with Con^- valence ratings after extinction training, with the latter being more pronounced for neural responses to Con^- ($p < .01$). Positive associations were evident between amygdalar Con^--related responses and Con^+ valence and between right vlPFC responses to Con^- and CS_Con^+ valence. Finally, Con^+ contingency ratings after extinction correlated with $NoCS\_Con^+$ activation of sgACC / vmPFC.

4. Discussion

Experimental models of classical fear conditioning constitute powerful tools in the investigation of mechanisms underlying psychopathology, including neural underpinnings of anxiety and stress-related disorders. A broadened scope to the field of pain underscoring the role of associative learning and memory processes in shaping pain-related fear as an essential component of fear-avoidance models of chronic pain has been discussed for several decades (Lethem et al., 1983; Vlaeyen, 2015). However, knowledge about neural mechanisms remains incomplete, and existing experimental conditioning models have not captured crucial facets of interoceptive pain-related fear of relevance to visceral pain. In a novel context-dependent interoceptive conditioning paradigm with clinically-relevant visceral stimuli, we tested if benign interoceptive sensations can context-dependently turn into conditioned predictors of visceral pain, involving the central fear network. Our behavioral findings revealed that the context, in which interoceptive cues predicted visceral pain, acquired negative valence. Together with differential contingency awareness of context-pain contingencies, these results support contextual conditioning on emotional and cognitive levels, extending previous conditioning work with complex contextual cues (Andreatta et al., 2015; Genheimer et al., 2017; Kroes et al., 2017) for the first time to an interoceptive context-dependent conditioning paradigm.

Within the brain, interoceptive cues context-dependently recruited key regions of the central fear network, supporting our hypothesis. Specifically, CS experienced in the context in which they were paired with pain induced enhanced activation within the vmPFC, amygdala, and bilateral hippocampus. Hippocampal responses particularly to in-

teroceptive CS in the safe context were negatively related to CS valence ratings in both contexts and were positively associated with contingency ratings between the threat context and pain, suggesting hippocampus to be particularly involved in processing contextual information. A hippocampal-amygdala circuitry in encoding threat-related contextual memories is increasingly well-characterized (Baeuchl et al., 2015; Chaaya et al., 2018; Kim and Cho, 2020). Findings from animal models indicate that vmPFC interacts with both regions within this circuit in the formation of hippocampal contextual and amygdala-mediated emotional memories (Zelikowsky et al., 2014). Interestingly, while behavioral data supported associative learning of context properties in terms of evaluative responses regarding valence and contingencies, the context alone did not induce differential neural activation during acquisition training. Derived from animal models and an increasing number of human fear conditioning studies, several processes have been described to be involved in the acquisition and expression of contextual information (Maren et al., 2013). Within this framework, contextual conditioning can be induced by a confrontation with an aversive stimulus within a particular context, resulting in the acquisition of contextual anxiety as a property of the danger context itself (e.g., Genheimer et al., 2017). Presenting unsignaled US in one context and US signaled by a predictive cue in another context allows a direct comparison of contextual anxiety and cue-induced fear, underlying mechanisms, and modulating factors (Grillon et al., 2006; Marschner et al., 2008; Stegmann et al., 2019; Zidda et al., 2018). Importantly, however, the context may also acquire modulatory characteristics signaling a relationship between a distinct cue and the US (Armony and Dolan, 2001), serving to retrieve CS-related information within each context in which it is experienced. In light of a comparable approach chosen herein involving contexts and interoceptive visceral cues in compound to predict pain or safety from pain, the observed central activation pattern suggests that, rather than directly serving a predictive function, contexts represented occasion setters (Fraser and Holland, 2019; Trask et al., 2017). Occasion setters do not elicit conditioned responses by themselves but rather exhibit a modulatory role to support flexible responding to CS (Urcelay and Miller, 2014). As such, contextual information likely disambiguated interoceptive CS, thereby gating the acquisition of pain-predictive value and triggering activation of the fear network in response to CS in a danger but not in a safety context. Notwithstanding broad implications for various psychopathologies (Fraser and Holland, 2019), occasion setting has thus far mainly been investigated in animal models (Holland and Bouton, 1999; Trask et al., 2017), and remains widely unexplored in the field of pain, despite its putative relevance to maladaptive pain-related responses, such as avoidance behavior (De Houwer et al., 2005; Declercq and De Houwer, 2008).

Our paradigm also allowed for analyses of differential responses to contexts when expected interoceptive cues remained absent. Here, an enhanced recruitment of amygdala together with a posterior proportion of dorsal ACC in the danger compared to the safety context emerged. As a core region of the salience network, ACC is crucially involved in a flexible deployment of attentional resources in the face of salient internal and external information with a core function to restore homeostatic states (Seeley, 2019). This includes the adaptive enhancement of attentional resources during learning, particularly in the presence of prediction errors (Bryden et al., 2011), in line with a particular role of the dACC in the appraisal and expression of learned fear (Milad and Quirk, 2012) as well as in conflict-monitoring (Etkin et al., 2011). Together with a possible role of ACC in maintaining remote contextual memories (Maren et al., 2013), these findings may indicate that a contextual memory trace was in fact established, becoming relevant to the individual only when the interoceptive predictor remains absent during the acquisition of interoceptive pain-related fear. This finding together with an observed association between ACC activation and pain contingencies in the safe context suggests an adaptive shift in attentional focus depending on predictive information available during visceral pain-related learning, as a putative mechanism contributing to interoceptive hypervigilance. Together, findings from interoceptive context-dependent acquisition of visceral pain-related fear indicate that contextual information may induce a hypervigilant state in which benign GI signals are centrally processed as predictors of impending threat, recruiting key regions of the central fear network.

During extinction training, the context-dependent differential activation of the fear network in response to interoceptive CS was no longer evident. Further, at the conclusion of extinction training, context valence and contingency ratings were comparable between contexts, supporting effective inhibitory learning. Analyses of context-related neural activation revealed enhanced responses of amygdala together with vmPFC and vlPFC to contexts previously predictive of pain, in support of our hypothesis postulating the involvement of regions tightly linked to processes of emotion regulation during extinction learning (Milad and Quirk, 2012; Sotres-Bayon et al., 2006). Exploratory analyses indicated enhanced involvement of vlPFC in context-related processing to be related to positive valence of the previously acquired safe context. In keeping with the assumption of attentional processes contributing to the observed activation patterns during context-dependent acquisition training, these findings may indicate an attentional shift from interoceptive CS acquiring salience due to their predictive value towards contextual information during extinction training. They further extend the above-mentioned notion that a context-dependent memory trace was indeed acquired during acquisition, becoming relevant to the individual not only when interoceptive cues remain absent during acquisition, but also when CS quickly cease differential predictive value in the absence of US during extinction, rendering contextual information more salient. The assumption that contextual information engages attentional resources particularly when distinct sources of prediction are limited is consistent with evidence supporting direct contextual control of extinction (Bouton, 2004; Trask et al., 2017). It is further in line with the well-known role of vmPFC and vlPFC in reappraisal, emotion regulation, and higher-order attentional control (Shiba et al., 2016), with a regulatory impact of these prefrontal nodes on the amygdala (Buhle et al., 2014; Wager et al., 2008). Responses of amygdala to the safe context further correlated with negative valence of the danger context at the end of the extinction phase, as indicated in our exploratory correlational analyses. The observed involvement of amygdala in CS-related processing during acquisition and in response to only contextual input during extinction may therefore also reflect distinct mechanisms, in accordance with animal findings documenting a role of basolateral amygdala in contextual control and some support for its contribution in the expression of occasion setting properties (Fraser and Holland, 2019). In light of this first evidence from animal models and our observations, the assumption of occasion setting characteristics of contexts may hold true also for the extinction phase. Of note, the hippocampus is considered to play a critical role in contextual encoding (Ji and Maren, 2007), a region which was recruited herein during the acquisition phase, but did not show differential activation during extinction. However, previous findings from human neuroimaging support a distinct role of the hippocampus in extinction memory recall, when contextual information is crucial to determine whether a reactivation of the fear memory or the competing extinction memory trace is warranted, rather than in extinction learning (Hermann et al., 2016; Kalisch et al., 2006; Milad et al., 2007).

Two unexpected behavioral results deserve further discussion. Contingency ratings, while supporting awareness of pain-predictive properties of Con^{+}, demonstrated a substantial overestimation of contingencies between pain and Con^{-}, indicating a diminished awareness of contextual safety properties across experimental phases. One possible explanation for this phenomenon can be derived from preparedness theory (Mineka and Ohman, 2002), postulating that an association between a predictor and an aversive outcome is more readily established when the predictor is fear-relevant. At the same time, such predictors are considered to be “contraprepared” for establishing safety-related associations, as recently highlighted for interoceptive CS showing resemblance to the US in experimental models of panic disorder (De Cort et al., 2017;

Pappens et al., 2013, 2012; Schroijen et al., 2015). Fear-relevant interoceptive CS herein occurring in both danger and safety contexts may have thus hampered effective safety learning, which is particularly interesting given first evidence supporting altered pain-related safety learning in chronic pain (Both et al., 2017; Meulders et al., 2015), including interoceptive visceral pain conditions (Icenhour et al., 2015b). Our exploratory correlational findings lend preliminary support for prefrontal / cingulate activation to be differentially related to this contingency overestimation. Particularly during acquisition, enhanced involvement of pdACC in response to the danger context was associated with lower, i.e. more accurate ratings of pain contingencies in the safe context. On the other hand, activation of sgACC / vmPFC during extinction was related to higher, i.e. overestimated Con^{+} contingency ratings following this phase in full absence of painful stimuli. While our findings from acquisition support attentional and regulatory processes to be involved in an accurate evaluation of safety properties of the context in the face of threat, future research elucidating this phenomenon is warranted.

Further, unlike previous observations documenting substantial changes in valence of exteroceptive visual predictors induced by pain-related fear conditioning (Gramsch et al., 2014; Icenhour et al., 2015a; Kattoor et al., 2013), valence of interoceptive cues herein remained widely stable, and CS were evaluated as rather pleasant across phases. One possible explanation could be that CS and US were not only repeatedly experienced, but also rated in close temporal proximity, possibly leading to a contrast effect in terms of CS evaluations in direct relation to substantially more aversive US. On the other hand, the relative pleasantness of CS also supports a clear differentiation to US from the same modality with respect to not only their intensity, but also their emotional valence to the individual. It appears promising for future studies to incorporate additional measures related to this emotional dimension, particularly threat or fear. Further elucidating these intriguing phenomena may provide valuable insight also with respect to inter-individual variability in context-dependent learning and extinction of relevance from conceptual and clinical perspectives alike.

In clinical reality, visceral pain experiences are often accompanied by comparatively “mild” interoceptive perceptions, especially in patients. These are by themselves not evaluated as harmful, yet could under certain circumstances be able to trigger defensive responses including fear and interoceptive hypervigilance. Our findings strongly support this notion, demonstrating that visceral sensations that are in their own right not evaluated as problematic symptoms, can through associative learning come to involve the central fear network when experienced in a context associated with visceral pain. Although the current findings from young and healthy participants call for cautious interpretations with respect to clinical implications, they lend first support that in patients with chronic visceral pain, innocuous gut signals may, modulated by the environment in which they occur, trigger a hypervigilant state and contribute to symptom exaggeration and increased suffering. Ultimately, mechanisms of interoceptive learning and modulations by contextual occasion setting properties may play a crucial, yet often overlooked role not only conceptually, but also clinically in recurrent and relapsing symptoms and in long-term treatment failure in disorders of gut-brain communication.

Conclusions

Building on this first evidence from a proof-of-concept study in a sample of young healthy volunteers, future research on contextual interoceptive learning as a possible contributor to interoceptive hypervigilance in disorders involving the gut-brain axis is warranted and appears highly promising. Extended approaches could thereby not only further elucidate the relevance of contextual control, including occasion setting, in interoceptive visceral pain-related fear learning and memory processes, but may also shed light on the role of prediction errors in shaping attentional processes during interoceptive excitatory and inhibitory learning. Given recent approaches to implement exposure-based treatment options in chronic visceral pain conditions (Craske et al., 2011; Ljótsson et al., 2014), a further investigation of underlying neurocircuitry, relevant modulators, and putative predictors of vulnerability but also resilience to specific learning phenomena could considerably advance the field and help to refine therapeutic approaches. Finally, relapse of pain-related fear and its maladaptive consequences after successful treatment is a common risk also in chronic pain (Meulders, 2020) and is likely driven by highly context-dependent phenomena, such as renewal effects. In the current interoceptive context-dependent conditioning paradigm, such extensions appear vital to elucidate neural underpinnings of context-related interoceptive memory reactivation with putative relevance to long-term efficacy of exposure-based treatment in disorders of the gut-brain axis.

Author statement

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Declaration of Competing Interest

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118229.

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