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Does pain modality play a role in the interruptive function of acute visceral compared with somatic pain?

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Abstract

Acute pain captures attentional resources and interferes with ongoing cognitive processes, including memory encoding. Despite broad clinical implications of this interruptive function of pain for the pathophysiology and treatment of chronic pain conditions, existing knowledge exclusively relies on studies using somatic pain models. Visceral pain is highly prevalent and seems to be more salient and threatening, suggesting that the interruptive function of pain may be higher in acute visceral compared with somatic pain. Implementing rectal distensions as a clinically relevant experimental model of visceral pain along with thermal cutaneous pain for the somatic modality, we herein examined the impact of pain modality on visual processing and memory performance in a visual encoding and recognition task and explored the modulatory role of pain-related fear and expectation in 30 healthy participants. Despite careful and dynamically adjusted matching of stimulus intensities to perceived pain unpleasantness over the course of trials, we observed greater impairment of cognition performance for the visceral modality with a medium effect size. Task performance was not modulated by expectations or by pain-related fear. Hence, even at matched unpleasantness levels, acute visceral pain is capable of interfering with memory encoding, and this impact seems to be relatively independent of pain-related cognitions or emotions, at least in healthy individuals. These results likely underestimate the detrimental effect of chronic pain on cognitive performance, which may be particularly pronounced in acute and chronic visceral pain.

Keywords: Visceral pain, Somatic pain, Interruptive function, Memory, Pain perception, Fear, Expectation

1. Introduction

Pain constitutes a highly salient warning signal that draws attention to potentially threatening situations, especially potential tissue damage, thus promoting fear and protective behavior. As defined by its interruptive function, pain frequently interferes with ongoing cognitive processes by capturing and redirecting attentional resources.[10] This "interruptive function of pain" has been indicated for acute experimental[4,13,14,35] and clinical pain[37] as well as for chronic pain,[16,38] demonstrably affecting working memory, visual processing, and attentional switching.[36]

Top–down factors, such as the expectation of pain-related impairment[13,53,54] or fear of pain,[7] as well as bottom–up factors, like the affected body site, likely determine the extent of pain–cognition interference. For example, experimental pain stimuli applied to the hand versus the face elicited different levels of pain-related fear[49,51,52] and differentially interfered with visual encoding and memory performance.[50,51] However, all of these studies used exteroceptive rather than interoceptive experimental models of acute pain.

With a prevalence of up to 25%, intermittent interoceptive abdominal pain constitutes one of the most common pain conditions[6] and is a key symptom of chronic visceral pain conditions.[31] Interoceptive visceral pain differs from exteroceptive somatic pain with respect to various aspects. Both pain modalities share common brain representations but importantly also show genuine processing differences,[2,60] which presumably shape differential responding at the behavioral level. Visceral stimuli, for instance, are perceived as more unpleasant and threatening than intensity-matched somatic pain stimuli[22]; they tend to show reduced perceptual habituation[22,67] and induce enhanced conditioned responses on the behavioral and neural levels,[2,23] presumably because of their high salience and threat level. These results suggest that interoceptive and exteroceptive pain might also differ with respect to other aspects of pain–cognition interactions, namely, the interruptive function of pain. To date, research addressing potential differences in cognitive interference induced by visceral and somatic pain and the

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 163 (2022) 735–744

http://dx.doi.org/10.1097/j.pain.0000000000002418

modulatory role of related cognitions, such as expectation and fear of pain, is lacking.

This study, therefore, compared the interruptive function of acute pain across modalities, with a focus on memory encoding and recognition in healthy participants. We implemented established experimental pain models for the visceral and somatic modality, respectively. Here, stimulus intensities were matched to perceived unpleasantness not only before testing but also dynamically adjusted to ensure comparable unpleasantness levels across time to exclude possible differences on outcomes resulting from different levels of unpleasantness. With respect to outcomes, participants performed a visual categorization task while receiving either no pain, visceral pressure pain, or somatic cutaneous heat pain during the simultaneous presentation of neutral images. This task was followed by a surprise recognition task without any painful stimulation. We expected stronger detrimental effects of visceral than somatic pain on recognition performance. Furthermore, we explored the role of expectations, pain-related fear, and other pain-related cognitions on the interruptive function of pain within and across modalities and assessed whether pain ratings developed differently between modalities during the task.

2. Methods

2.1. Participants

Data were acquired in N = 39 healthy participants at the University Hospital of Essen, Germany. A screening procedure including a clinical examination 0 to 3 days before the experiment ensured the following inclusion criteria: normal or corrected-to-normal eyesight; no known history of neurological, psychiatric, gastrointestinal, and pain-related disorders; and no color blindness. During the screening visit, after written informed consent and introduction to the experimental procedures, participants underwent a general and digital rectal examination by a trained physician (J.K.-B.) to detect any gastrointestinal disorders (eg, hemorrhoids), which led to the participant's exclusion. Afterwards, participants were screened for depression (Center for Epidemiologic Studies Depression Scale [CES-D], no subject had to be excluded because of values above the cutoff of 18) and completed questionnaires on pain-related psychological processing, as well as state and trait anxiety (see below).

All participants gave written informed consent and were free to withdraw from study participation at any time. The study had been approved by the local ethics committee in Essen, Germany (17-7486-BO). Participants received monetary compensation for their study participation. The study was not preregistered. All experimental phases, ie, matching of pain stimuli, encoding, and recognition phase, were performed consecutively inside the magnetic resonance imaging scanner. For details, see *Experimental Procedures*.

2.2. Experimental procedures

On the day of the experiment, participants were positioned in a magnetic resonance imaging scanner (data to be reported elsewhere) and underwent a matching procedure of visceral and thermal pain stimuli as described below to determine individually calibrated stimuli matched in subjective unpleasantness. Before the beginning of the categorization task, participants provided ratings of their expectations of the interaction between pain and task performance and of their fear of pain. All ratings were provided separately for visceral and somatic pain. Afterwards, participants were familiarized with the categorization task by performing one trial of each condition (ie, 9 categorization trials). After that, the actual categorization task and surprise recognition task succeeded.

2.3. Experimental paradigm

2.3.1. Categorization task

To probe the impact of visceral and somatic pain stimuli on cognitive task performance, we used a modified version of an established visual encoding paradigm consisting of a categorization task (ie, encoding) and a surprise recognition task.[14,51] This task has previously been demonstrated to be reliably modulated by somatic pain.[13,15,50,51,54] Moreover, it allows assessing the effects of pain on different cognitive domains (eg, visual perception and implicit memory encoding). During the categorization task (duration 25-30 minutes), participants were presented images of natural scenes showing either living or nonliving objects. Concurrently to this visual stimulation, participants were exposed to 3 stimulation conditions, ie, individually calibrated visceral or somatic painful stimuli or a control condition, in which no pain stimulus was applied, using a within-subject design. Importantly, visceral and somatic pain stimulation was dynamically adapted during the categorization task to ensure comparable levels of pain unpleasantness during the whole task (see below). In detail, the categorization task included 63 neutral images of living and nonliving objects (see "Visual stimuli") that were reduced in visibility (33%) to increase task difficulty.[14] Twenty-one images were presented without any painful stimulation (control condition). The remaining 42 images were presented with either concurrent visceral or somatic painful stimulation, respectively. Thus, each condition comprised 21 trials that were presented in blocks of 3 images (each condition 7 blocks) in a pseudorandomized order with no more than 3 images of one category (ie, living or nonliving) and no more than 2 blocks of one condition in a row.

The trial structure of the categorization task was as follows: presentation of a white fixation cross (variable duration of 20-30 seconds), start of painful stimulation (in case of a visceral or somatic pain trial), image 1 (2.5 seconds), presentation of a white fixation cross (1.5 seconds), image 2 (2.5 seconds), presentation of a white fixation cross (1.5 seconds), image 3 (2.5 seconds), end of painful stimulation/return to baseline (in case of a visceral or somatic pain trial), presentation of a white fixation cross (2-4 seconds), and a rating period for pain unpleasantness and pain intensity (5-10 seconds each, see below) with 2 to 4 seconds black screen between both ratings. The intertrial interval between blocks was set to 18 to 28 seconds. For details, see **Figure 1**. The participants were asked to categorize each image as living or nonliving by pressing one of 2 buttons as quickly as possible without compromising on accuracy (categorization task). Unpleasantness and pain intensity ratings of each pain stimulus were performed on a trial-by-trial basis.

2.3.2. Recognition task

Subsequently, a surprise recognition task (duration 25-30 minutes) followed to investigate the modality-specific interruptive effect of visceral and somatic pain on object encoding. Here, all previously presented images intermixed with the same number of new images (126 images total) were presented. All images were now presented in full visibility. Participants were asked to indicate a known (old) or unknown (new) image by giving their confidence

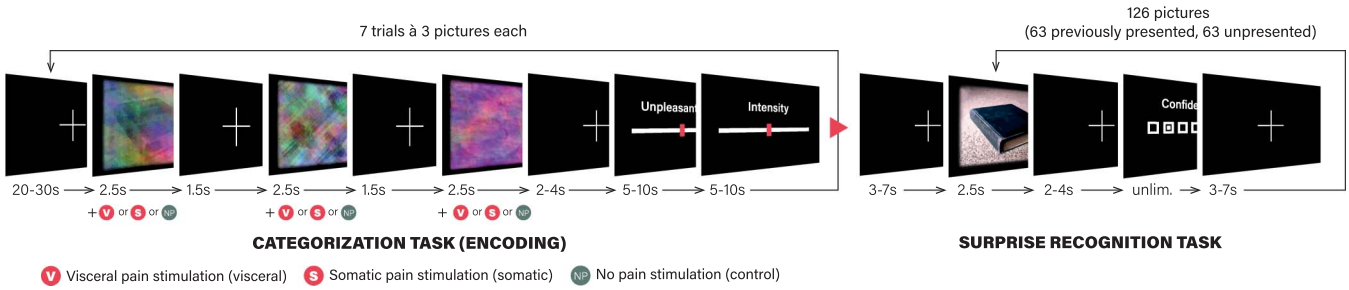

Figure 1. Experimental paradigm. During the categorization task (encoding phase, left), 63 images of living or nonliving objects were presented with reduced visibility (33%) for 2.5 seconds each. One example trial is shown. In two-thirds of the trials, somatic pain stimuli or visceral pain stimuli matched in unpleasantness were applied. Pain unpleasantness and intensity were rated after each trial. During the recognition task (right), 126 images (63 old and 63 new) were presented in full visibility. Participants indicated a known (old) or unknown (new) image by giving a confidence rating on a 6-point scale.

rating on a 6-point confidence scale (anchors "surely old"–"surely new"). Images were presented for 2.5 seconds each followed by a fixation cross (2-4 seconds), the confidence rating (no time limit), and a fixation cross (3-7 seconds) before the next image was shown. During the recognition task, no painful stimulation was applied (see **Fig. 1** for details).

2.3.3. Stimuli

The presentation of the visual stimuli, application of the thermal and visceral pain stimuli, and recording of the behavioral data were performed using Matlab version 2015b (MathWorks, Natick, MA).

2.3.4. Visual stimuli

Visual stimuli were presented on a back-projection screen located behind the MR scanner, which could be seen through a mirror that was attached to the head coil. They consisted of images showing natural scenes with living (eg, animals) or nonliving (eg, items of everyday life) objects. One hundred thirty-five images with neutral valence, that have been used in our laboratory before,[14,51] were presented. Images presented during the categorization task were reduced in visibility (33%) using a scrambling routine as described previously by Rose et al.[46] The visual angle of the images was 11.6° × 8.4°, and their outer edges were smoothed (28 mm full-width at half-maximum [FWHM] isotropic kernel) to embed them into a black background.

2.3.5. Pain stimulation

A magnetic resonance imaging-compatible thermal device (PATHWAY model CHEPS; Medoc, Israel) was used to apply painful heat stimuli with a plateau duration of 12.5 seconds. The CHEPS thermode (27 mm diameter) was attached to the left volar forearm. The baseline temperature was set to 32°C. Heating and cooling rates were set dependent on the chosen stimulation temperature and pressure (see below) to match rise and fall times for both pain stimuli. Rectal distensions were performed with a pressure-controlled barostat system (modified ISOBAR 3 device; G & J Electronics, Ontario, Canada), as previously used.[2,23,48] An infinitely compliant catheter-affixed polyethylene bag of cylindrical shape with a diameter of 10 cm and a maximal volume of 600 mL when fully inflated was attached to a rectal tube with an outer diameter of 5 mm. The balloon was inserted into the rectum after lubrication, with the distal bag margin 5 cm beyond the anal verge. Intermittent phasic isobaric rectal balloon distensions with a duration of 12.5 seconds at the plateau were delivered. Stimulation duration for both pain stimuli was identical within each participant and between experimental phases (ie, calibration, matching procedure, and categorization task, see below). Temperature rise and fall times were individually adjusted to match inflation and deflation times of the rectal distension stimuli, which depended on individual target pressures. To ensure the presentation of visual stimuli at the plateau of the pain stimuli, image presentation started with an individual delay after the onset of pain stimulation.[23]

2.3.6. Matching procedure and adaption during categorization task

Visceral and heat pain stimuli were individually calibrated and dynamically adjusted throughout the course of the experiment, to yield comparable pain unpleasantness levels of 70 on a 0 to 100 Visual Analog Scale (VAS, anchors 0 = "not unpleasant at all" and 100 = "unbearably unpleasant") during the task. Owing to Koenen et al.[22] showing that at comparable intensity levels, participants perceived higher unpleasantness for visceral compared with somatic pain, and because pain unpleasantness comprises a more affective, disturbing component,[42] we decided to match for individual pain unpleasantness. This is also in line with previous studies from our group using the same experimental paradigm while investigating 2 different modalities, ie, pain and tone.[14]

The application of temperature and pressure stimuli was accomplished through external control using the Psychtoolbox V3[5] in Matlab. Both stimulus modalities, ie, temperature and pressure, were calibrated using the same adaptive staircase algorithm[21]: Starting from a minimum (temperature: 40.5°C/ pressure: 1 mm Hg), stimulus intensities were applied in increasing steps of 0.5°C/5 mm Hg until the target unpleasantness rating of 70 on a 0 to 100 VAS was reached or exceeded. On reaching target unpleasantness, stimulus intensities were reduced in steps of the same size, until unpleasantness ratings fell below target, again. In all experimental procedures, after every stimulus application, stimulus intensity (ie, heat or pressure) returned to baseline (ie, 32.0°C, 0 mm Hg, resp.) before the next stimulus presentation. The stepwise increases and decreases were repeated until 2 such step reversals above and below the rating target were accomplished. The procedure then was continued for 2 further reversals at step sizes of 0.3°C/3 mm Hg and, subsequently, for 2 more reversals at step sizes of 0.3°C/ 2 mm Hg. Finally, the calibrated stimulus intensity was calculated by averaging the last 4 stimulus intensities applied. Calibration was terminated prematurely if a total of 4 maximum (48.0°C/

50 mm Hg) or minimum (40.5°C/1 mm Hg) stimulus intensities were applied without achieving the target rating. The order of calibration (temperature first and pressure first) was randomized across participants.

During the categorization task, pressure and temperature stimuli were automatically and dynamically adapted to yield the target unpleasantness rating of VAS 70 and thus to ensure stimulus matching. To accomplish this, during each trial, the stimulus was adjusted by 2 mm Hg (visceral pain stimulation) or 0.3°C (heat pain stimulation) as soon as the unpleasantness rating target was exceeded or undercut. For ethical considerations, stimulus intensities were limited for both thermal and visceral stimulation during all procedures.

2.3.7. Questionnaires

The Center for Epidemiological Studies Depression Scale,[43] German version: ADS-K,[17] was used to screen for depressive symptoms (cutoff value = 18). To ensure no incidences of gastrointestinal symptoms due to functional or organic gastrointestinal diseases, participants filled a questionnaire quantifying frequency and severity of typical upper and lower gastrointestinal symptoms as part of the screening procedure.[27] To account for potential influences of pain-related and affective cognitions, participants filled the following questionnaires: (1) short version of the Pain Anxiety Symptom Scale: PASS20-D,[32] German version[64]; (2) Pain Catastrophizing Scale,[57] German version[29]; and (3) State-Trait Anxiety Depression Inventory.[30] All questionnaires were analyzed following their respective manuals.

2.3.8. Outcome variables

Behavioral main outcome variables within the categorization task comprised the percentage of correct responses, reaction times (RTs) of correct responses, pain unpleasantness, and intensity ratings. Unpleasantness and pain intensity ratings were performed using a 0 to 100 VAS (VAS, anchors VAS unpleasantness 0 = "not unpleasant at all" and 100 = "unbearably unpleasant", anchors VAS intensity 0 = "not painful at all" and 100 = "unbearably painful").

For the recognition task, the percentage of images classified as old (pooled across confidence levels "sure old"–"rather old" [1, 2, and 3 of the confidence scale]) and new (pooled across confidence levels "sure new"–"rather new" [6, 5, and 4 of the confidence scale]) was calculated. The discrimination index d'[55] was calculated for all experimental conditions separately to account for false alarm rates using the formula d' = z(hit rate) − z(false alarm rate). Higher values of d' indicate better discrimination and therefore better recognition memory.

Moreover, subjective ratings of fear of pain, the expected interruptive function on task performance, and the expected pain reduction during task performance were recorded separately for visceral and thermal pain (ie, fear of pain: "How fearful are you regarding the upcoming thermal/pressure pain stimulation?", VAS anchors: 0 = "not fearful at all" and 100 = "extremely fearful"; expectation of the impact of pain on task performance: "Please indicate how the perception of thermal/pressure painful stimulation will influence your visual task performance," VAS anchors: −50 = "strong performance decrease," 0 = "no influence," 50 = "strong performance increase"; and expectation of the impact of task performance on pain perception: "Please indicate how performing the visual task will influence your thermal/pressure pain perception," VAS anchors: −50 = "strong pain reduction," 0 = "no influence," 50 = "strong pain increase"). All ratings were provided separately for visceral and somatic pain.

2.4. Statistical analyses

Statistical analyses were performed with the software R.[44] Results with a $P < 0.05$ are considered as statistically significant. In case of nonnormally distributed data and residuals, the nonparametric Wilcoxon signed-rank test or linear mixed models on ranked data were performed.

2.4.1. Categorization and recognition task

Reaction time and percentage of correct responses during the categorization task were checked for outliers (2 SD ± mean, no outliers found), and RT > 2.5 seconds was not recorded.[14] Data were analyzed using linear mixed model analyses. Models were calculated separately and contained fixed effects for the factor condition and individual unpleasantness ratings for each condition separately as a covariate of no interest to account for potential differences in pain unpleasantness. D′ scores were checked for outliers using the Rosner Test function in R (package EnvStats[33]) and analyzed using linear mixed model analyses. The model contained fixed effects for the factor condition and individual unpleasantness ratings as a covariate of no interest.

For both experimental phases and all outcome variables, the following variables were included separately as potential covariates into the model: the individual difference between expectation ratings regarding the interruptive effect of visceral and somatic pain stimuli, differences in modality-specific expectation ratings of changes in pain perception, differences in modality-specific pain-related fear, and pain-related cognitions, eg, pain catastrophizing. All models were estimated according to the restricted maximum likelihood approach, and the best model was chosen according to the Akaike information criterion (AIC) (maximum likelihood approach) as indicated by the χ^2 test for significance used for model comparison.

2.4.2. Expectation and fear ratings

The paired *t* test was calculated to examine differences in expectation of pain-related interruptive effects during task performance, expectation of pain modulation during task performance, and pain-related fear between both pain conditions.

2.4.3. Pain unpleasantness and pain intensity ratings

Each experimental condition consisted of 7 trials resulting in 7 applied temperatures and 7 pressures, respectively, that were adapted on a trial-by-trial basis. Using linear mixed model analyses, we tested whether adapted temperatures and pressures developed differently over the course of the experiment. For that purpose, temperatures and pressures were standardized (ie, z-transformation) to ensure comparability because of the different measurement units (ie, °C and mm Hg).

To further account for potential differences in time-related changes in pain unpleasantness and pain intensity ratings for both experimental pain conditions, linear mixed model analyses were performed on pain unpleasantness and intensity ratings separately. Note that no observed differences in pain unpleasantness ratings would support the success of our adaptive stimulation procedure.

Table 1

Behavioral data separately for each experimental condition.

	Visceral pain condition	Somatic pain condition	Control condition
Pain unpleasantness	63.55 ± 8.40	60.47 ± 10.59	10.30 ± 14.27
Pain intensity	50.62 ± 14.37	64.13 ± 11.14	10.32 ± 13.96
Pain-related fear	50.0 ± 26.30	47.61 ± 28.62	—
Expected interruptive function of pain	−12.0 ± 14.74	−14.40 ± 14.20	—
Expected pain modulation by task performance	−10.78 ± 14.65	−5.89 ± 10.98	—
Correct responses in % in the categorization task	86.5 ± 9.8	85.2 ± 10.2	85.1 ± 14.2
RT in s in the categorization task	1.24 ± 0.45	1.22 ± 0.45	1.31 ± 0.48

Pain unpleasantness and intensity: 0-100 VAS (anchors VAS unpleasantness 0 = "not unpleasant at all" and 100 = "unbearably unpleasant"; anchors VAS intensity 0 = "not painful at all" and 100 = "unbearably painful"). Pain intensity ratings were significantly lower for visceral compared to thermal pain. Fear and expectation ratings: Anchors VAS pain-related fear: 0 = "not fearful at all" and 100 = "extremely fearful"; anchors VAS expected interruptive function of pain: -50 = "strong performance decrease", 0 = "no influence", 50 = "strong performance increase"; anchors VAS expected pain modulation by task performance: -50 = "strong pain reduction", 0 = "no influence", 50 = "strong pain increase"). All data provided in mean ± SD. RT, reaction time.

All models comprised fixed effect factors for condition and time as well as their interaction. It was tested whether the model containing a random intercept for each participant and allowing variation for the factors condition, time, and subjects by adding random slopes for these factors improved model fit. We thus allowed for a subject-specific variation of intercepts, ie, starting points, and slopes, ie, subject-specific developments, over time for each condition. The individual, modality-specific expectation ratings of pain–cognition interference and modality-specific pain-related fear as well as pain-related cognitions, eg, pain catastrophizing, were included as potential covariates into the model. The models were estimated according to the restricted maximum likelihood approach. We decided for the best model according to the AIC as indicated by the χ^2 test for significance used for model comparison.

3. Results

Although n = 39 participants have been enrolled, data from n = 9 participants had to be excluded because of technical failure (n = 5) and pain unpleasantness ratings not reaching the predefined baseline level during calibration (n = 4, see below for details). Thus, data from n = 30 participants were analyzed (all right-handed, 7 males; age in years: 25.8 ± 8.8 [M ± SD]). Questionnaire results of our study sample of healthy, young participants did not reveal any anomalies in depression, anxiety, and pain-related cognition scores according to the respective questionnaire manuals (data not shown). We provide confirmatory results of an extended sample including n = 6 additional participants from the corresponding pilot trial using very similar experimental procedures in the supplement (available at http://links.lww.com/PAIN/B448).

3.1. Categorization task

As intended by our adaptive procedure (ie, unpleasantness rating-based adjustments of visceral and somatic pain stimuli), and as a prerequisite to allow the comparison of modality-specific interruptive effects of pain, there were no significant differences in pain unpleasantness between visceral and somatic pain stimuli during the categorization task (t[387.0] = −0.50, $P = 0.62$, d = −0.05). Categorization performance was not compromised by concurrent painful stimulation. Percentages of correct responses did not differ between the 3 experimental conditions, while controlling for subjective modality-specific unpleasantness (all $P > 0.4$). For the RT, nonparametric testing on ranked data was performed. When controlling for individual unpleasantness, results showed no differences in RT between conditions (all $P > 0.2$). None of the other covariates improved model fit and were thus not significantly related to the interruptive effects of pain on categorization performance. Please see **Table 1** for details.

3.2. Recognition task

The false alarm rate was 34% ± 13% (mean ± SD). When controlling for subject-specific and pain modality-specific unpleasantness ratings, we found impaired recognition performance (d') for the visceral pain condition (β = 0.61 ± 0.22 [95% CI 0.52-0.84]) compared with the thermal pain condition (β = 0.74 ± 0.21 [95% CI 0.65-0.97]) with medium effect sizes without reaching significance (t[56.39] = −1.84, $P = 0.07$, d = −0.49). There were no significant differences in d' between the control condition (β = 0.77 ± 0.09 [95% CI 0.62-0.94]) and both pain conditions (visceral: t[67.74] = −0.85, $P = 0.40$, d = −0.21; thermal: t[67.54] = −0.16, $P = 0.87$, d = 0.04). None of the tested covariates improved model fit and, thus, did not significantly modulate the effects of pain on recognition performance. Results are displayed in **Figure 2**.

3.3. Pain-related ratings

Pain-related expectation and fear ratings are given in **Table 1**. Neither expected interference of pain with task performance nor pain-related fear ratings differed significantly between visceral and thermal pain (expected interference: t[29] = 0.66, $P = 0.51$; fear ratings: t[29] = 0.42, $P = 0.68$). However, participants expected visceral pain to be more prone to perceptual modulation when performing the categorization task, meaning they expected a stronger reduction in perceived pain for visceral than somatic pain (t[29] = −2.28; $P = 0.03$).

Interestingly, as shown by exploratory analyses, the individual pain-related fear of thermal pain was inversely correlated with the expectation of task performance during thermal pain ($r = −0.41$, $P = 0.03$) indicating higher fear being associated with increased expectations of impaired task performance. Moreover, higher fear of thermal pain correlated significantly with expected thermal pain increase during task performance ($r = 0.37$, $P = 0.04$). These correlations were not present for visceral pain (all $P > 0.05$).

3.4. Pain unpleasantness and pain intensity ratings

When performing analyses of the development of pain unpleasantness ratings, including random slopes did not improve

model fit (Δ AIC = 0.8, $P = 0.07$), indicating no better prediction of the data when allowing for random variance of changes over time or the experimental conditions. Unpleasantness ratings increased throughout the categorization task for both pain modalities with medium effect sizes (temperature: β = 2.79 ± 0.63 [95% CI 1.56-4.02]; t[387.0] = 4.43, $P < 0.001$, d = 0.38; pressure: β = 2.34 ± 0.63 [95% CI 1.11 – 3.58]; t[387.0] = 3.72, $P < 0.001$, d =0.38). For exploratory analyses, the actual stimulus intensity, ie, the z-transformed respective pressure or temperature, was included on a trial-by-trial basis as a covariate of interest into the model (Δ AIC = 1.9, $P = 0.04$). Results showed higher unpleasantness ratings with higher stimulus intensities (β = 6.91 ± 2.91 [95% CI 1.11-12.57]; t[411.92] = 2.38, $P = 0.02$, d = 0.23). Importantly, this association was equally present in all experimental conditions, ie, no interaction of *time* × *condition* × *stimulus intensity* ($P > 0.7$).

For pain intensity, the model including random slopes for the factor time best predicted the data (Δ AIC = 21.5, $P < 0.001$). Pain intensity significantly increased over time for both pain stimuli with medium effect sizes (temperature: β = 2.02 ± 0.59 [95% CI 0.86-3.19]; t[79.96] = 3.38, $P = 0.001$, d =0.50; pressure: β = 1.33 ± 0.60 [95% CI 0.16-2.50]; t[79.97] = 2.23, $P = 0.03$, d = 0.49). Moreover, as expected, because of previous reports on higher pain unpleasantness at comparable intensity levels for visceral then somatic pain, pain intensity ratings were significantly lower for visceral pain with a medium effect size (Δ β = 10.75 ± 4.18 [95% CI 18.13-3.36]; t[121.02] = 2.57, $P = 0.01$, d = 0.47) but there were no significant differences between conditions in the development of pain intensity over time (Δ β = −0.69 ± 0.77 [95% CI −2.34 to 0.96]; t[329.00] = −0.90, $P = 0.37$, d = −0.10). Please see **Figure 3** for results. Taken together, these exploratory analyses revealed comparable time-related developments of unpleasantness and intensity ratings for both pain modalities. Importantly, as expected, higher pain intensities for somatic as compared with visceral pain are needed to achieve comparable unpleasantness, which is why we had decided to match for unpleasantness in this study.

3.5. Temperatures and pressures yielding Visual Analog Scale 70

To investigate how the abovementioned changes in perception were driven by actual stimulus intensities, we performed analyses on the time-related changes in the used temperatures and pressures. The model including subject-specific random slopes and the factors *condition* and *time*, ie, allowing for variance of development over time between the experimental conditions, best predicted the data as compared with the model without random slopes (Δ AIC = −845.71, $P < 0.001$). We observed an increase in temperature and pressure needed to yield VAS 70 over the course of the experiment with large effect sizes (pressure: β = 0.05 ± 0.01 [95% CI 0.02-0.08]; t[36.65] = 4.08, $P < 0.001$, d = 1.35; temperature: β = 0.08 ± 0.01 [95% CI 0.05-0.1]; t[36.65] = 5.98, $P < 0.001$, d =1.98) (**Figure 4**). Interestingly, we found a significant interaction for the factors *time* and *condition*. Visceral as compared with thermal stimuli had to be less adjusted over time (t[329.0] = −2.84, $P = 0.004$, d = −0.31). Moreover, including the difference in pain-related fear between both conditions as a covariate into the model (Δ AIC = −12.45, $P < 0.001$) showed that this lower increase for the visceral compared with thermal stimuli was significantly modulated by pain-related fear. Specifically, the increase of visceral compared with thermal pain stimuli over time to yield VAS 70 was lower in individuals with higher levels of visceral compared with thermal pain-related fear (Δ β: −0.0009 ± 0.0003 [95% CI −0.0003 to −0.002]; t [332.80] = −2.91, $P = 0.004$, d = −0.32).

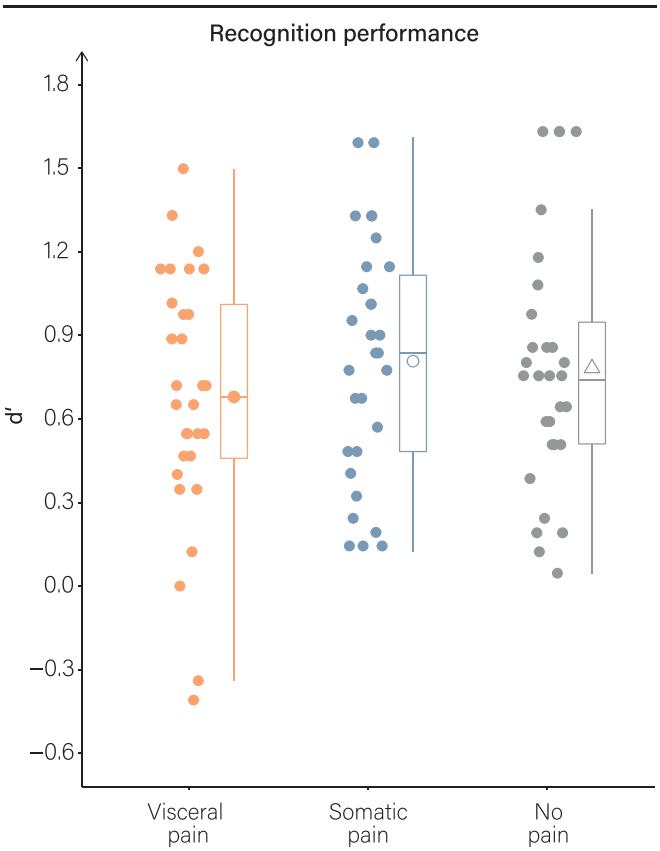

Figure 2. Recognition performance (d') for the 3 experimental conditions. Displayed are boxplots and means. Single dots display individual subject data. For illustration of raw recognition performance (ie, percentage of correct hits), see supplement, available at http://links.lww.com/PAIN/B448.

4. Discussion

This study was designed to assess the interruptive function of acute visceral vs somatic pain using a visual encoding and recognition task and to explore the role of pain-related cognitions and emotions on the interruptive function of pain within and across modalities. To this end, we implemented well-established experimental pain models for the visceral and somatic modality, respectively, in a within-subject design and herein for the first time used pain stimuli that were not only a priori individually calibrated and matched to perceived unpleasantness but were also dynamically adjusted to comparable unpleasantness levels over the course of repeated stimulations. This procedure allowed for complementing and extending our earlier work on mechanisms of pain across body sites[51] and modalities[22] and generating novel insight into the development and relation of objective stimulus intensities and subjective measures of perception over time.

As intended, stimulus matching as well as repeated unpleasantness rating-based adjustments of visceral and somatic pain stimuli successfully ensured comparable levels of pain unpleasantness during the encoding phase. Interestingly, however, to yield the predefined level of unpleasantness (ie, VAS 70), the somatic modality required greater adjustment (ie, increases) of stimulus intensities, possibly reflecting a greater habituation for the somatic than for the visceral pain modality. A lack of—or a reduced—perceptual habituation to repeated acute visceral pain is consistent with the notion of its exceptional biological salience and corroborates earlier observations in the same pain models,[22] together supporting cumulating evidence on pain modality-specific peripheral and central mechanisms along the gut–brain

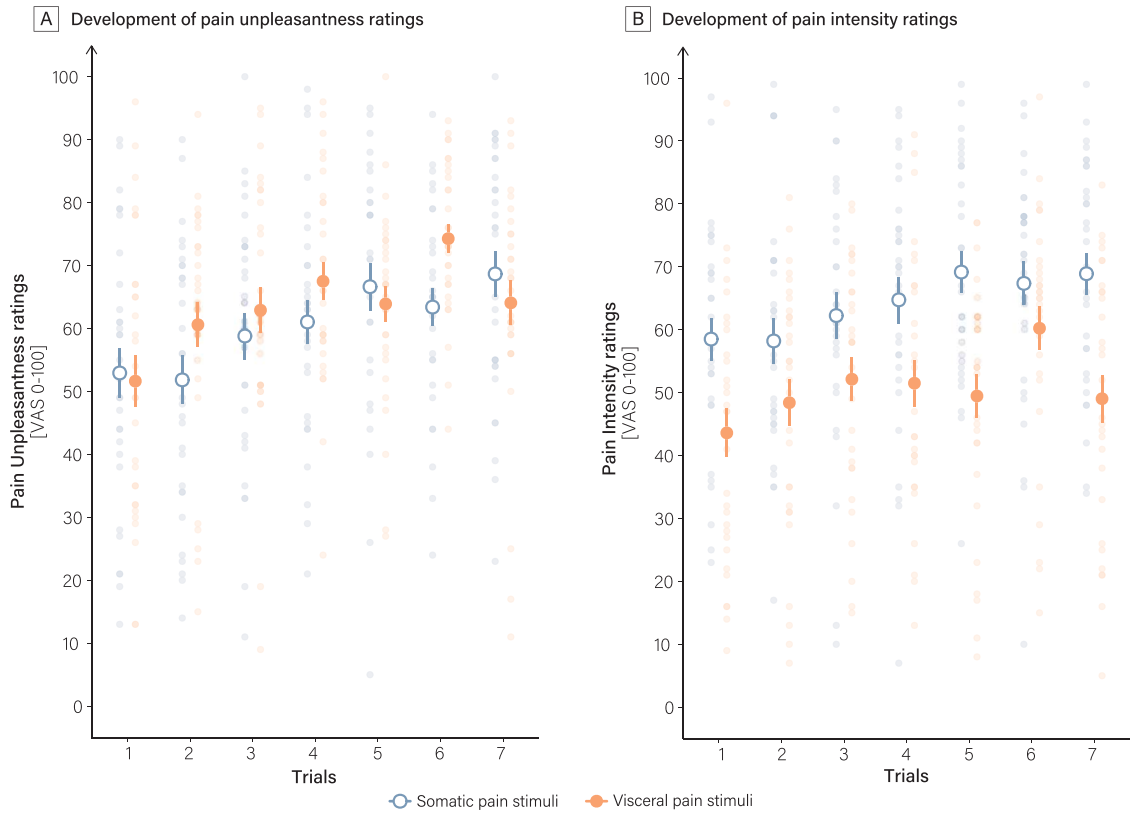

Figure 3. Development of pain unpleasantness (A) and pain intensity (B) ratings for somatic and visceral pain stimuli over the course of the categorization task. Displayed are mean and SE (error bars). Light dots display single-subject data. For details on data distribution, please see supplement, available at http://links.lww.com/PAIN/B448.

axis.[22,60] However, because cognitive load reportedly decreases pain perception,[14,45,51] our results on the development of unpleasantness and pain intensity ratings in this unique paradigm do not represent the natural course and only allow for an indirect assessment of perceptual habituation or sensitization.

In support of our hypothesis, we observed a decrease in recognition performance (ie, d') for images previously paired with visceral compared with somatic pain. Although this effect did not reach statistical significance, analyses revealed a medium effect size, which is particularly noteworthy because it was clearly not attributable to modality-specific differences in unpleasantness and observable despite lower perceived pain intensity for the visceral compared with the somatic pain stimuli. In other words, our experimental approach is unique and arguably highly conservative in that it excluded or at least minimized effects of modality-specific differences in unpleasantness, which have repeatedly been reported, resulting herein in greater pain intensity for the somatic modality. Hence, visceral pain may be capable of impairing memory encoding in healthy participants even at relatively lower intensity, possibly because of its higher salience for biological relevance and implicit threat.[22,34,56] Our results in this highly controlled study design with its predictable and short-lasting acute pain stimuli matched for pain unpleasantness likely underestimate effects in real scenarios of acute and especially of chronic pain. Because we presented images after a continuously and relatively slow increase in stimulus intensity at the plateau of painful stimulation, the experimental condition of each trial, ie, before first image presentation, was cued and hence predictable. We previously documented the impact of predictability on behavioral and neural measures in the same visceral pain model,[26] suggesting the possibility that herein participants might have used adaptive strategies to counteract performance impairment during pain perception.[51] Probably, in a design with unannounced pain trials and faster stimulus ramps, which is however limited for the rectal distension model, the interruptive effect of visceral pain would be even more pronounced, even in healthy individuals.

In this article, experimental somatic pain did not lead to recognition impairment compared with the control condition, as observed in a very similar study,[14] in which the interruption of experimental thermal pain was compared with an unpleasant auditory stimulus. The experience of 2 different pain modalities, of which one—visceral pain—seems to be more threatening and salient,[22] might have altered the interruptive function of somatic pain and reduced the effect.[58,65] We have previously investigated the interruptive function of 2 different pain locations, ie, face and hand pain, in a comparable functional magnetic resonance imaging study,[51] in which we found similar effects of hand and face pain on recognition performance but increased compensatory neural resource activation for the more salient face pain. This study, however, only compared both pain stimuli and did not include a control condition. How the experience of acute pain from 2 modalities may impact on the interruptive function of pain on the behavioral and neural levels needs to be investigated further, especially in light of chronic pain patients commonly reporting multiple types of pain from various bodily locations.

With respect to the putative role of pain-related cognitions and emotions, especially expectations and fear and their role in pain modulation, particularly in placebo and nocebo effects,[3,63] we observed no differences between visceral and somatic pain in the expected interference of pain with task performance or in pain-

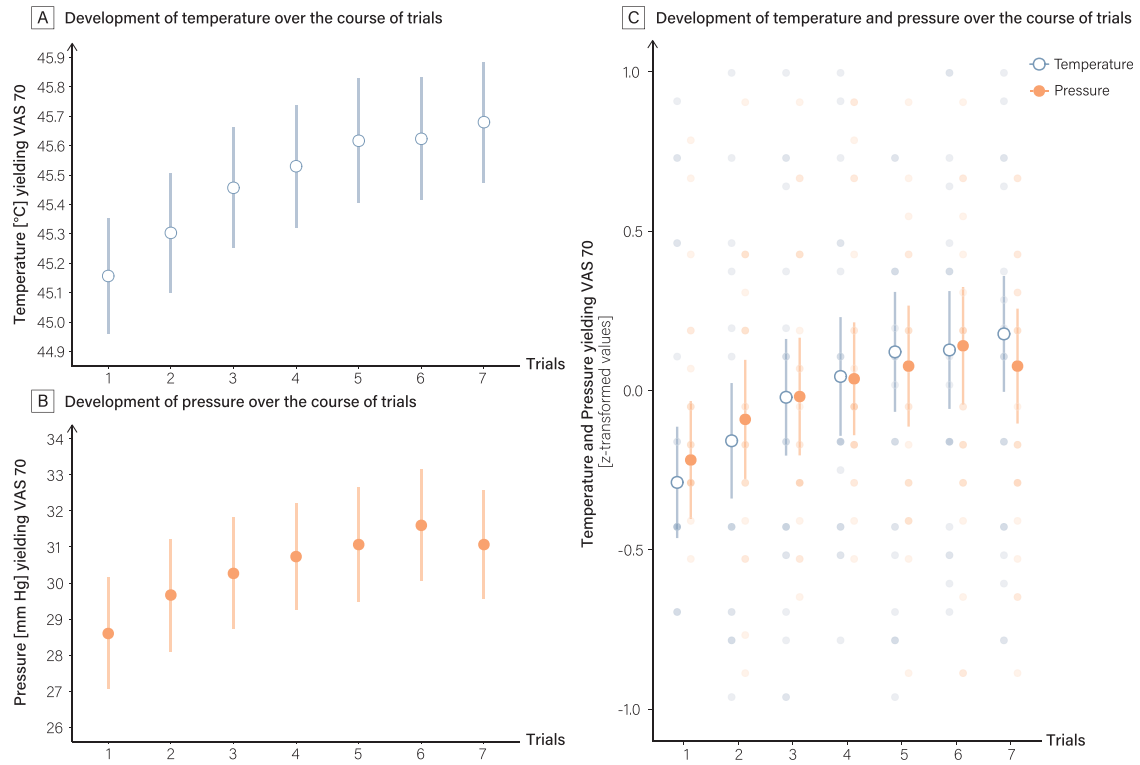

Figure 4. Development of temperature (A) and pressure (B) and z-transformed values of temperature and pressure (C) over the course of the categorization trials. Displayed are mean and SE (error bars). Light dots display single-subject data. For details on data distribution, please see supplement, available at http://links.lww.com/PAIN/B448.

related fear ratings. Interestingly, participants expected the cognitive demands of performing a challenging task to exert a greater impact on visceral pain perception. In other words, healthy participants a priori believed that cognitive engagement would reduce visceral pain to a greater extent than somatic pain. Little experimental evidence on the interrelation between neurocognitive demands, expectations, and pain perception exists for the visceral modality, despite growing knowledge regarding placebo mechanisms.[11,47,48] The present data are the first to suggest that there indeed may exist differences between pain modalities, which is interesting given the high incidence of visceral symptoms even in healthy individuals who seem to expect that cognitive demands more readily modify visceral than somatic perception. Whether this expectation regarding the modulation of pain by factors like distraction or other engaging cognitive activities is altered in patients with chronic pain constitutes an interesting future direction given the role of cognitive-behavioral treatment approaches including psychoeducation in patient groups such as irritable bowel syndrome (IBS). Moreover, although fear ratings did not differ between both conditions, higher fear of visceral but not somatic pain correlated with a flatter increase in administered pressure during the task, which might indirectly indicate less habituation of visceral pain perception in healthy participants reporting higher fear of visceral pain and further supporting the important role of fear of pain in the visceral pain context.[22,61,67]

These results have to been seen in the light of some limitations. First, our sample size is comparingly small, limiting statistical power and, hence, our ability to detect possible small effects. Although the addition of data from more participants as a supplementary analysis (available at http://links.lww.com/PAIN/B448) corroborated our main results, further studies with larger samples are needed to replicate and expand on the present results. Second, the peripheral or central mechanism(s) along the complex and bidirectional gut–brain axis underlying the enhanced interruptive function of visceral compared with somatic pain remain uncertain. Based on our methodological approaches and initial evidence, the stage is now set for basic and translational studies assessing mediators, moderators, as well as clinical implications to help close the gap between neurocognition and an evolving field on exteroception vs interoception.[24,60] This will help elucidate the role of salience and preparedness, with fascinating implications for our understanding of different facets of symptom perception and cognition.

Given the frequent incidence of cognitive impairment in chronic pain patients,[39,41] one could assume that the observed visceral pain-related recognition impairment under highly controlled experimental conditions in healthy participants might be more pronounced in chronic pain,[9,62] especially in chronic visceral pain conditions such as IBS or ulcerative colitis. Persistent or recurrent gut dysbiosis and gut inflammation have been discussed to induce systemic inflammation and neuroinflammation in several key brain areas, thereby promoting cognitive impairments.[9] Although cognitive impairment and altered pain-related attentional biases have been described in patients suffering from IBS,[8,28,66] experimental studies investigating the interruptive function of chronic pain at the mechanistic level are scarce.[1,25,38,40] To date, studies regarding cognitive effects of chronic visceral pain only reported enhanced pain-related attentional control[18,28,59,66] or a deficit in episodic visuospatial memory in patients with IBS.[20] Moreover, patients with IBS show increased conditioned responses and contingency awareness compared with healthy controls,[19] suggesting altered associative learning in the chronic visceral pain context. Such alterations in learning have been reported to influence the development and maintenance of chronic pain.[12] Our study is the first to examine

the effect of experimentally induced visceral compared with somatic pain on memory functions in healthy individuals. In contrast to other pain conditions, especially chronic visceral pain with its high affective und unpleasant component and its high rate of psychiatric comorbidities, could compromise episodic memory, adding to impaired everyday functioning and increasing the emotional burden of chronic visceral pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank Ashtar Hashim and Leonie Kerkmann for their help with data collection, Christoph Ritter and Nina Theysohn for technical/medical support, and Matthias Gamer and Laura Ricarda Koenen for their insightful advice. This study was funded by the German Research Foundation (Gefördert durch die Deutsche Forschungsgemeinschaft (DFG), Projektnummer 422744262—TRR 289). J. Kleine-Borgmann was supported as a Clinician Scientist within the University Medicine Essen Academy (UMEA) program, funded by the German Research Foundation (Gefördert durch die Deutsche Forschungsgemeinschaft [DFG], Projektnummer FU356/12-1) and the Faculty of Medicine, University of Duisburg-Essen. The conducted research was not preregistered with an analysis plan.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B448.

Article history:
Received 14 January 2021
Received in revised form 13 July 2021
Accepted 19 July 2021
Available online 29 July 2021

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