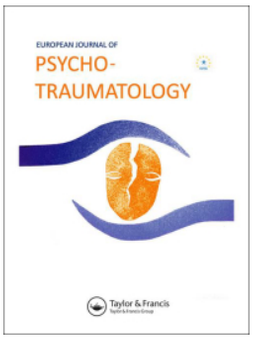

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BASIC RESEARCH ARTICLE

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Neural processing of audiovisual and painful analogue trauma and its relationship with subsequent audiovisual and pain intrusions

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ABSTRACT

Background: Posttraumatic stress disorder and medically unexplained pain frequently co-occur. While pain is common during traumatic events, the processing of pain during trauma and its relation to audiovisual and pain intrusions is poorly understood.

Objective: Here we investigate neural activations during painful analogue trauma, focusing on areas that have been related to threat and pain processing, and how they predict intrusion formation. We also examine the moderating role of cumulative lifetime adversity.

Methods: Sixty-five healthy women were assessed using functional magnetic resonance imaging. An analogue trauma was induced by an adaptation of the trauma-film paradigm extended by painful electrical stimulation in a 2 (film: aversive, neutral) x 2 (pain: pain, no-pain) design, followed by 7-day audiovisual and pain intrusion assessment using event-based ecological momentary assessment. Intrusions were fitted with Bayesian multilevel regression and a hurdle lognormal distribution.

Results: Conjunction analysis confirmed a wide network including anterior insula (AI) and dorsal anterior cingulate cortex (dACC) being active both, during aversive films and pain. Pain resulted in activation in areas amongst posterior insula and deactivation in a network around ventromedial prefrontal cortex (VMPFC). Higher AI and dACC activity during aversive>neutral film predicted greater audiovisual intrusion probability over time and predicted greater audiovisual intrusion frequency particularly for participants with high lifetime adversity. Lower AI, dACC, hippocampus, and VMPFC activity during pain>no-pain predicted greater pain intrusion probability particularly for participants with high lifetime adversity. Weak regulatory VMPFC activation was associated with both increased audiovisual and pain intrusion frequency.

Conclusions: Enhanced AI and dACC processing during aversive films, poor pain vs. no-pain discrimination in AI and dACC, as well as weak regulatory VMPFC processing may be driving factors for intrusion formation, particularly in combination with high lifetime adversity. Results shed light on a potential path for the etiology of PTSD and medically unexplained pain.

Procesamiento neuronal del trauma analógico audiovisual y doloroso y su relación con intrusiones audiovisuales y dolorosas posteriores

Antecedentes: El trastorno de estrés postraumático y el dolor medicamente inexplicable suelen coexistir. Si bien el dolor es frecuente durante los eventos traumáticos, el procesamiento del dolor durante el trauma y su relación con intrusiones audiovisuales y dolorosas no se comprenden bien.

Objetivo: En este trabajo investigamos las activaciones neurales durante un trauma análogo doloroso, centrándonos en áreas relacionadas con el procesamiento del dolor y la amenaza y en cómo predicen la formación de intrusiones. También examinamos el papel moderador de la adversidad acumulada a lo largo de la vida.

Métodos: Fueron evaluadas sesenta y cinco mujeres sanas utilizando imágenes de resonancia magnética funcional. Se indujo un trauma analógico mediante una adaptación del paradigma de película de trauma ampliado con estimulación eléctrica dolorosa en un diseño de 2 (película: aversiva, neutral) x 2 (dolor: dolor, sin dolor), seguida de una evaluación audiovisual y de intrusión del dolor durante 7 días mediante una evaluación ecológica momentánea basada en eventos. Las intrusiones se ajustaron con regresión multinivel Bayesiana y una distribución log normal de obstáculos.

ARTICLE HISTORY

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KEYWORDS

Pain; trauma film; affective neuroscience; posttraumatic stress disorder; intrusion; fMRI; lifetime adversity; childhood adversity

PALABRAS CLAVE

Dolor; película de trauma; trastorno de estrés postraumático; intrusión; fMRI; neurociencia afectiva; adversidad a lo largo de la vida; adversidad en la infancia

HIGHLIGHTS

- AI and dACC play a common role for both trauma- and pain-processing.
- In combination with high lifetime adversity, higher AI and dACC aversive film processing was associated with higher audiovisual intrusion frequency, whereas weaker AI and dACC pain discrimination enhanced the chance for pain intrusions.
- Weak regulatory VMPFC activity in aversive situations increased both audiovisual and pain intrusion formation.

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Resultados: El análisis de conjunción confirmó una red amplia que incluye la ínsula anterior (IA) y la corteza cingulada anterior dorsal (CCAd) activa tanto durante películas aversivas como durante el dolor. El dolor resultó en activación en áreas entre la ínsula posterior y la desactivación en una red alrededor de la corteza prefrontal ventromedial (CPFVM). Una mayor actividad de la IA y la CCAd durante una película aversiva>neutra predijo una mayor probabilidad de intrusión audiovisual a lo largo del tiempo y predijo una mayor frecuencia de intrusión audiovisual, particularmente para los participantes con gran adversidad a lo largo de la vida. Una menor actividad de IA, CCAd, hipocampo y CPFVM durante el dolor>sin dolor predijo mayor probabilidad de intrusión de dolor, particularmente para los participantes con gran adversidad alo largo de la vida. Una activación débil reguladora de la CPFVM se asoció con una mayor frecuencia de intrusiones audiovisuales y de dolor.
Conclusiones: El procesamiento mejorado de la IA y CCAd durante las películas aversivas, la escasa discriminación entre dolor y ausencia de dolor en IA y CCAd, así como el débil procesamiento regulador de la CPFVM pueden ser factores impulsores de la formación de intrusiones, particularmente en combinación con una gran adversidad a lo largo de la vida. Los resultados arrojan luz sobre una posible vía para la etiología del TEPT y el dolor medicamente inexplicable.

1. Introduction

Posttraumatic stress disorder (PTSD) is a complex psychiatric condition characterized by avoidance, negative changes in thinking and mood, alterations in physiological arousal and emotional reactions, and intrusive and distressing memories that replay elements of traumatic events, leading to profound emotional distress and impairment in daily functioning (American Psychiatric Association, 2013). Previous research has predominantly focused on the impact of real-life traumatic events on the development of intrusions and subsequent PTSD (Ehlers & Clark, 2000; James et al., 2016; Ozer et al., 2003). Our study aimed at shedding light on a less explored avenue – the influence of physical pain, in conjunction with trauma-film exposure – on the formation of intrusions in healthy individuals.

A well-accepted theoretical model attempting to explain that both PTSD and pain symptoms mutually maintain each other following a traumatic event (Sharp & Harvey, 2001), is supported by research showing that PTSD and pain symptoms predict each other at subsequent time points (Carty et al., 2011; Jenewein et al., 2009; McAndrew et al., 2019; Ravn et al., 2018). Its key assumption is that pain serves as a trauma reminder, triggering re-experiencing of the traumatic event. Likewise, others have advanced the idea that, vice versa, pain in PTSD patients can also be understood as somatic re-experiencing triggered by trauma reminders (Asmundson & Katz, 2009). Somatic re-experiencing has been described as a form of somatosensory memory where pain experienced at the time of trauma is later re-experienced, despite the absence of persisting injury. Recently, Macdonald et al. (2018) have provided support for this notion by demonstrating that 49% of PTSD patients indeed re-experience physical pain experienced at the time of the trauma when reminded of their trauma. In addition, the number of body areas of physical pain experienced during the trauma was associated with a higher number of pain re-experiences. In a similar vein, Franke et al. (2022) showed that painful somatosensory intrusions after analogue trauma might, just as audiovisual intrusions (Franke et al., 2021), result from conditioning processes, providing further support for the conceptualization of posttraumatic pain as a type of 'pain intrusion' elicited by trauma reminders. Besides the important contribution of conditioning processes to the aetiology of audiovisual and pain intrusions, cognitive–behavioural models also indicate that peritraumatic processing plays a crucial role in intrusion formation (e.g. Ehlers & Clark, 2000). This is supported by research in trauma-exposed persons (Ozer et al., 2003) as well as by analogue trauma studies using highly aversive film-clips in a laboratory setting, which allows investigating processes during traumatization, not being possible in retrospective clinical studies (Holmes & Bourne, 2008). Neural models of PTSD suggest that hyperactive threat processing (e.g. in the amygdala, dorsal anterior cingulate cortex (dACC), and anterior insula (AI)) as well as hypoactive regulatory efforts (e.g. in the ventromedial prefrontal cortex (VMPFC)) are associated with PTSD symptom severity (Fragkaki et al., 2016; Pitman et al., 2012; Rauch et al., 2006).

Studies mimicking traumatic experiences using aversive films (the so-called trauma-film paradigm) revealed heightened amygdala and rostral ACC activity during encoding of scenes that later become intrusive (Bourne et al., 2013), whereas dACC and parahippocampal gyrus played a central role during the encoding of negative images in participants with intrusions (Battaglini et al., 2016). Both encoding and involuntary recall of intrusive memories were associated with inferior frontal cortex activity (Clark et al., 2016). Miedl et al. (2018) revealed enhanced neural threat processing (comprising dACC,

amygdala, and AI) during viewing of aversive film clips relative to a neutral control condition, which was modulated by estradiol levels and hormonal contraception. Exploratory analyses showed that heightened rostral ACC, middle, and inferior frontal cortex activity during aversive film-viewing was associated with lower intrusion frequency three months after the experiment, suggesting regulatory frontal activity to attenuate long-term intrusion formation. In addition to peritraumatic neural processing, lifetime adversity constitutes a trait-like risk factor for developing PTSD on re-exposure to trauma (Breslau et al., 1999). Findings from neuroimaging studies suggest that lifetime adversity influences neural processing of threat detection and emotion regulation (Teicher et al., 2016). Recently, we could show that in participants with high lifetime adversity, neural activity of the threat processing structures (involving AI and dACC) during aversive processing predicted intrusions (Rattel, Miedl, et al., 2019). Enhanced sensitivity to trauma cues in a network including AI and dACC was linked to intrusion frequency in healthy women (Miedl et al., 2020), further emphasizing the central role of these brain regions in analogue trauma processing and intrusion formation. As similar underlying mechanisms are proposed for different sensory modalities, higher peritraumatic neural processing could not only be a good predictor for audiovisual but also for pain intrusions (Clark & Mackay, 2015). Importantly, the regions, including ACC and insula, are not only active during audiovisual threats, but are also responsive to painful stimulation and linked to higher levels of self-reported pain (Reddan & Wager, 2018), implicating to also study their impact on the development of pain intrusions.

Besides script-driven imagery (e.g. Danböck et al., 2024; Pole, 2007) and fear conditioning approaches (e.g. Blechert et al., 2007; Suarez-Jimenez et al., 2020) with PTSD patients, experimental models in healthy humans have induced an analogue trauma by 'traumatic' films depicting accidents or interpersonal violence and have thus focused on peritraumatic affective, cognitive, and neural factors contributing to intrusion formation. Yet, as physical pain constitutes an inherent feature of many traumatic events, it might be important to also consider the influence of physical pain and its neural concomitants. During painful stimulation, research has linked pain to higher activation in AI, ACC, somatosensory cortex, ventrolateral thalamus, and posterior insula, and lower activation in VMPFC and precuneus (Wager et al., 2013). Moreover, recent work has revealed associations between medial prefrontal activity and pain modulation as well as pain chronification (Ong et al., 2019). Pain representations (Bräscher et al., 2020), like other sensory input (Van den Bergh et al., 2017), are shaped top-down by cognitive and emotional factors and pain may even be present in the absence of nociceptive input (Franke et al., 2022). Altered processing of the body image, impaired multisensory integration, and deficient interoceptive processing have been associated with chronic pain, indicating that neurobehavioral processes might be crucial for maintaining pain (Flor, 2012). Indeed, a systematic review of functional and structural alterations in patients suffering from chronic low back pain found evidence for increased activity in areas involved in emotional and cognitive modulation such as dACC, medial prefrontal cortex, and insula in response to painful stimulation (Kregel et al., 2015).

The present study combined fMRI (functional magnetic resonance imaging) recordings of brain activity during trauma film viewing with and without painful stimulation with assessment of audiovisual and pain intrusion formation. By utilizing film-clips depicting severe interpersonal violence in combination with painful stimulation – thus portraying potentially traumatic events – we expected enhanced activity in typical threat- and pain-processing regions such as insula and dACC, memory processing regions as hippocampus, as well as emotion/pain regulating areas such as VMPFC. Furthermore, we predicted heightened threat and pain processing, as well as reduced regulatory processing to be linked to enhanced intrusion formation. Since our previous trauma film study confirmed lifetime trauma exposure as a moderating variable for neural threat processing and subsequent audiovisual intrusions (Rattel, Miedl, et al., 2019) we were additionally interested in the role of individual differences in lifetime adversity.

2. Methods and materials

2.1. Participants

Sixty-eight healthy female participants were recruited for this study via public announcements (internet and university). Only women were tested due to previous research indicating that men respond differently to aversive film clips (Wilhelm et al., 2017). A sufficient number of men for assessing gender differences could not be included due to monetary and time constraints. Exclusion criteria were blood-injection-injury phobia, self-report of psychosis, psychotropic medication use, substance abuse/dependency, bipolar disorder, serious medical conditions, anxiety, depression, PTSD, or history of traumatic head injury. Further exclusion criteria were extensive media consumption of violent and/or medical content (more than three times a week) and poor sleep quality (score of seven or higher on the Pittsburgh Sleep Quality Index; Buysse et al., 1989). All participants indicated to feel currently mentally and physically resilient. Having experienced traumatic events in the

past was not an exclusion criterion since this is quite common. Forty-one participants reported at least one potentially traumatic event (22 participants reported no traumatic event; see Figure S1) assessed after the ambulatory intrusion assessment with a modified version of the Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000) using LimeSurvey (Limesurvey GmbH, Hamburg, Germany). Two participants did not complete the TLEQ assessment. Trauma history was assessed on day 7 to avoid confrontation with traumatic experiences at the beginning of the experiment, which could potentially influence the results of the trauma-pain conditioning experiment. First, participants were asked to identify which, if any, from a list of 15 different kinds of traumatic experiences they had experienced by 'no' or 'yes'. The list included the following: Natural disasters, motor vehicle accidents, other accidents, warfare or combat, sudden death of a close friend or loved one, robbery involving a weapon, severe assault by an acquaintance or stranger, witness to assault by an acquaintance or stranger, threat of death or serious bodily harm, childhood physical abuse, witness to family violence, physical abuse by an intimate partner, sexual abuse, stalking, and others. If at least one experience had been reported, participants were asked to report how often they had experienced each affirmed trauma category. The total number of trauma experiences across all trauma categories per participant refers to the individual TLEQ sum score (cumulative lifetime adversity). For the TLEQ no Cronbach´s α was calculated because no singular underlying construct is being measured, but possible trauma experiences being independent from each other. For fMRI, exclusion criteria were pregnancy, ferromagnetic implants, other non-removable metal objects, and claustrophobia. Three participants had to be excluded due to technical problems at the MRI scanner. Thus, 65 participants (age: $M = 21.94$ years, $SD = 3.08$) were included in the final analyses and 63 participants for analyses involving TLEQ. Current psychopathology was assessed with the German versions of the Depression, Anxiety and Stress Scale – depression-scale (DASS-D; Nilges & Essau, 2015), the State-Trait-Anxiety Inventory (STAI-T; Laux et al., 1981), the Questionnaire of Dissociative Symptoms (QDS; Freyberger et al., 1998), and the Screening for Somatoform Symptoms-7 (SOMS-7; Rief & Hiller, 2003). Distribution of scores was typical for healthy samples for depressive symptoms, trait anxiety, dissociative symptoms, and somatoform symptoms: DASS-D, 7-items, total score 0–42: $M = 3.45$, $SD = 4.07$, Cronbach's $\alpha = .88$; STAI-T, 20 items, total score 20–80, $M = 38.22$, $SD = 8.54$, Cronbach's $\alpha = .90$; QDS, 44 items, total score 0–100%, $M = 7.46$, $SD = 5.99$, Cronbach's $\alpha = .93$; SOMS-7 ICD-10 somatization index, 14 out of 53 items, total score 0–14, M = 0.97, $SD = 1.56$, Cronbach's $\alpha = .85$. Scores suggesting clinical relevance are >10 for DASS-D (Nilges & Essau, 2015), >44 for STAI-T (Ercan et al., 2015), and >13 for QDS (Rodewald et al., 2006). Average ICD-10 somatization scores within the general population are $M = 1.1$ and $SD = 1.7$ (Rief et al., 2001). The study was approved by the local ethics committee, and participants provided informed consent before participation.

2.2. Procedure

Participation started with a demographic and psychometric screening and background information collection via online questionnaires. After pain calibration (for details see section 'Pain calibration procedure') and an eight-minute resting state fMRI each participant was exposed four times to each of the following conditions during fMRI: a neutral film without painful stimulation, another neutral film paired with painful stimulation, an aversive film without painful stimulation, and another aversive film paired with painful stimulation. The pairing of films (details see Supplement) with painful stimulation was counterbalanced across participants and stimuli were presented in pseudorandom order, with maximally two of the same conditions in a row. Intertrial-intervals ranged from 12–16s. As this study was part of a larger investigation, film-clips were preceded by an image resembling an element of the respective film-clip. Participants underwent another eight-minute resting state fMRI sequence at the end of the session, returned to the lab for another fMRI session 24 h later where participants saw the resembling images again, and reported pain and audiovisual intrusions during the following days using a smartphone application. Only data of the first fMRI session were analysed for this study. Ecological momentary intrusion assessment started immediately after the first fMRI session, with a total duration of seven consecutive days. Intrusions were defined as spontaneously occurring memories in form of pictures, bodily sensations, sounds, feelings, or thoughts regarding the painful stimulation or film-clips as well as sudden recurring physical sensations, thoughts, or feelings experienced while watching the film-clips or experiencing the painful stimulation. We instructed participants to register every intrusion in the e-diary app upon occurrence, i.e. in an event-based manner (Rattel, Grünberger, et al., 2019). We informed participants of the possibility that pain and film recollections could coincide and instructed them to decide whether their recollection was primarily of film clips or of painful sensations. We also instructed participants to record each intrusion in the e-diary app as it occurred, i.e. in an event-based manner. Finally, participants were instructed to provide a brief description of the

intrusion that occurred and of potential triggers in the e-diary application. To monitor compliance, participants received text message reminders for another questionnaire on the e-diary each day at 10 pm, where they were explicitly asked whether they had reported all intrusions throughout the day. In cases of noncompliance, participants were asked to retrospectively estimate the true number of intrusions which were then used to substitute the respective participants' event-based intrusion score of that day. E-diary compliance over seven days was 87.25%.

2.3. Pain stimulation and pain ratings

Electrical stimulation (E-Stim) was delivered to the inner surface of the left calf using a Digitimer DS7A constant current stimulator (Digitimer Ltd, Hertfordshire, England) via a concentric surface electrode with 7 mm diameter and a platinum pin (WASP electrode, Brainbox, Cardiff, UK). Stimulation started with film onset and was applied in a train of 7×1 s electrical pulses with varying interpulse intervals in order to produce stable stimulus intensities (Mouraux et al., 2014). Participants rated pain stimulation on a continuous scale from 0 to 10 (0, no sensation; 5, moderate pain; 10 maximally tolerable pain, Rance et al., 2014b), where maximally tolerable was defined as the point where participants would want to remove the electrode from their leg and stop the stimulation.

2.4. Pain calibration procedure

Before each session, E-Stim strength was individually calibrated while participants were seated on the MRI table, outside the coil. Following a well-established stepwise calibration procedure (Rance et al., 2014a), stimulation started at 0.2 mA and was increased by 0.2 mA until participants verbally reported (a) detection of the stimulus (detection threshold) and (b) noticeable pain (pain threshold). This pain threshold intensity was then stepwise increased by 5% until participants reported (c) their pain tolerance level. Stimulation intensity was adjusted to an intensity of 30% between pain threshold and pain tolerance. The calculated stimulation intensity was tested and, if necessary, adjusted to yield a pain rating of 6–7 (painful, but tolerable).

2.5. Ratings

At the end of the experiment on day one, participants also rated valence (0 = very pleasant, 10 = very unpleasant) and pain sensations (0 = not painful, 10 = maximum pain tolerance) for each of the four conditions (aversive pain, aversive no-pain, neutral pain, neutral no-pain).

2.6. FMRI recording

A 64-channel head/neck coil was used and functional images sensitive to BOLD contrast were acquired with a T2*-weighted gradient echo EPI sequence (TR = 1050 ms, TE = 32 ms, FOV = 192 mm, flip angle = 69°). Fifty-six slices with a slice thickness of 2.4 mm were acquired within the TR. Six dummy scans were acquired at the beginning of each functional run. Additionally, a gradient echo field map (TR 623 ms, TE 1 = 4.92 ms, TE2 = 7.38 ms) and a high-resolution (0.8 mm × 0.8 mm × 0.8 mm) structural scan with a T1-weighted MPRAGE sequence (TR = 2400 ms; TE = 2.24 ms) were acquired. Participants viewed the experiment through a head-coil–mounted mirror and sounds were presented via noise-shielding headphones.

2.7. FMRI data analyses

Functional magnetic resonance imaging data preprocessing and analysis were performed using SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom). First, the functional images were corrected for geometric distortions using the FieldMap toolbox, were realigned, unwarped, and slice time corrected to the onset of the middle slice. Structural images were segmented and normalized to MNI standard stereotactic space. The resulting parameters were then used for normalization of the previously co-registered functional images, which were resampled to isotropic 3 mm^3 voxels and smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel. Statistical analysis was performed in a random-effects model: In the first-level model, each event was convolved by a canonical hemodynamic response function. Regressors for the first-level model included images resembling elements of each film-clip (4s) and film-clip responses (16s). We also added the six rigid-body movement parameters determined from realignment from the respective session as covariates of no interest. For analyses the threshold was set to $p < .05$ corrected for multiple comparisons based on the familywise error rate (FWE) implemented in SPM with clustersize (k) $\geq$ 5 voxels. A FWE is a false positive anywhere in the Statistical Parametric Maps (SPMs). Thus, if we repeat the present experiment many times and generate SPMs, the proportion of SPMs containing FWEs is the FWE rate. A value of 0.05 means that, on average, 1 in 20 SPMs contains one or more false positives somewhere in the image. Whole brain analyses were run entering contrast images into a second-level random effects model applying a full factorial design with the factors film (aversive, neutral) and pain (pain, no-pain) as within-participant factors. Furthermore, conjunction analysis [conjunction null (Nichols et al., 2005)] was calculated using SPM12 to

assess common effects of pain>no-pain & aversive>neutral conditions ($P < .05$, FWE-corrected, k = 5). Details for performing conjunction analysis by selecting multiple contrasts during group analysis can be found in the SPM12 manual, pages 319–322: https://www.fil.ion.ucl.ac.uk/spm/doc/spm12_manual.pdf. In the results tables (Tables 1–7) multiple coordinates listed within a cluster refer to subclusters. There are two possibilities: (A) The subcluster is in the same anatomical region as the peak cluster, then no region is listed in the left column. (B) The subcluster is in a different anatomical region than the peak cluster, then this anatomical region is displayed in the left column.

Parameter estimates of each region of interest (ROI) were extracted with MarsBaR Toolbox within SPM. The signal was averaged across the entire cluster. For the VMPFC and hippocampus we used masks of WFU PickAtlas toolbox implemented in SPM. The dACC mask was built with the WFU PickAtlas toolbox using the procedures described by Cascio et al. (2015): it was defined as the union of Brodmann areas 24 and 32 (dilated to 2 mm), as well as the anterior, middle, and posterior cingulate masks from the AAL atlas. Then, Brodmann areas 8 and 9 were subtracted from this mask. Finally, this ROI was restricted to the voxels bounded by ($x = -16$ to 16, $y = 0$ to 33, and $z = 6$ to 52). For the anterior insula, we used an online atlas of functional ROIs (Shirer et al., 2012), created by applying FSL's MELODIC independent component analysis software (http://www.fmrib.ox.ac.uk/fsl/melodic/index.html). Posterior insula mask was defined as an 8 mm sphere around the peak coordinates [±36,−16,14] of a meta-analysis of 516 pain studies in the Neurosynth database (Yarkoni et al., 2011).

2.8. Statistical analyses

We computed Bayesian multilevel regression models (BMLMs) in R 4.0.3 (R Core Team, 2019) via the Stan-based brms package (Bürkner, 2017; Carpenter et al., 2017). Rating data (self-reported valence and pain) were fitted with ordinal (cumulative) BMLMs. Furthermore, the predictors pain and film were dummy coded (pain: no-pain = 0, pain = 1; film: neutral = 0, aversive = 1). Because we expected that the effects of pain and film could vary between participants, we added varying slopes for pain and film in all models to account for this potential variability.

As a main analysis, we examined whether brain responses to aversive>neutral and pain>no-pain contrasts predicted intrusions during daily life. We expected that the effect of day on intrusions (i.e. the decay of intrusions) could vary between participants and added a varying slope for the effect of day. To account for the inflation of zero intrusions in the data, daily-life intrusions were fitted with a hurdle lognormal distribution. With this approach, we fitted data in two parts where we (A) estimated the probability of not experiencing (i.e. zero) vs. experiencing (i.e. non-zero) intrusions (hurdle part, modelled with a Bernoulli distribution), referred to as 'probability of intrusion absence'; and (B) estimated the amount of (i.e. frequency of) intrusions>0 (lognormal part, modelled with a lognormal distribution) referred to as 'intrusion frequency'. We fitted separate models for the predictors AI, dACC, and VMPFC activity (details see Supplement) during aversive>neutral and pain>no-pain contrasts, respectively. In these models, we further added Day and TLEQ sum score as well as interactions between brain activity, day, and TLEQ sum score to model potential effects of analogue trauma on the persistence/decay of pain intrusions during daily life as well as effects of cumulative lifetime adversity. Predictors were centred and standardized before being entered in BMLMs: brain activity was centred to its respective mean, and Day was centred on the first 24 h day after the first fMRI session, i.e. on the second experimental day (see Supplement, Table S2 for Bayesian model specifications).

We report regression coefficients and, as recommended (Kruschke, 2014; Makowski et al., 2019; McElreath, 2020; see also Danböck et al., 2024 and Korem et al., 2022), 89% credible intervals (CIs), i.e. Bayesian confidence intervals. Eighty-nine percent CIs constitute intervals in which the respective parameter falls with 89% probability given the data observed, prior, and model assumptions. We consider effects as significantly different from zero if the CI does not include zero. We used weak- or non-informative default priors of brms whose influence on results is negligible (Bürkner, 2017, 2018). All BMLMs converged as indicated by common algorithms-agnostic (Vehtari et al., 2019) and algorithm-specific diagnostics (Betancourt, 2017). There were no divergent transitions, Rhat<1.01 and ESS>400 for all relevant parameters.

3. Results

3.1. Behavioural results

The analysis of valence ratings revealed significant main effects of film (b = 7.05, 89%CI = [5.94, 8.29]) and pain (b = 1.90, 89%CI = [1.30, 2.52]), and a significant film × pain interaction (b = −2.00, 89%CI = [−2.84, −1.18]). This was driven by a higher pain vs. no-pain difference only during neutral film-clips (pain>no-pain aversive; (b = −0.18, 89%CI = [−0.99, 0.55]); pain>no-pain neutral: (b = 2.01, 89%CI = [1.33, 2.82])). Pain ratings showed significant main effects of film (b = 4.71, 89%CI = [3.54, 6.03]) and pain (b = 7.59, 89%CI = [6.02, 9.52]), and a significant film × pain interaction (b = −3.94, 89%CI = [−5.22, −2.78]). This was driven by a weaker pain vs. no-

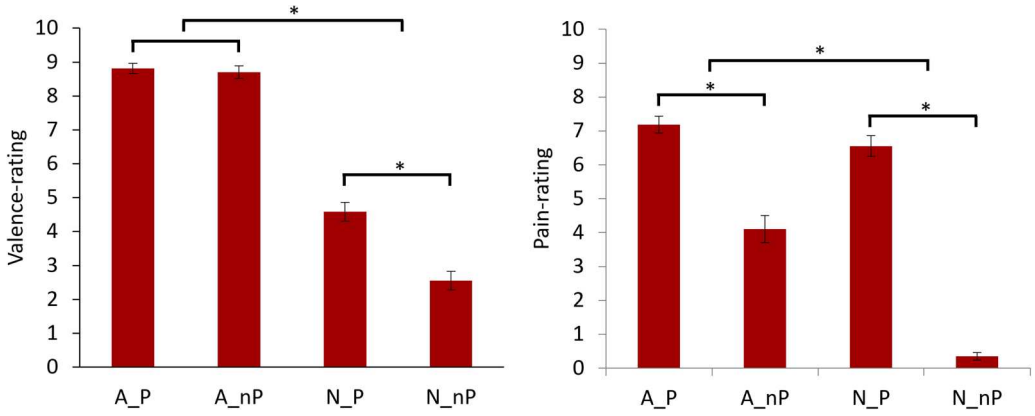

Figure 1. Left panel: Means ± standard error of post-experimental valence-ratings (0 = very pleasant, 10 = very unpleasant). Right panel: Means ± standard error of post-experimental pain-ratings (0 = not painful, 10 = maximally bearable; A_P = aversive pain, A_nP = aversive no-pain, N_P = neutral pain, N_nP = neutral no-pain, * denotes significant effect between conditions and interaction).

pain difference during aversive film-clips compared to neutral film-clips (pain>no-pain aversive; (b = 2.99, 89%CI = [1.89, 4.44])); pain>no-pain neutral: (b = 7.85, 89%CI = [5.52, 10.81]) Figure 1.

3.2. FMRI results

The aversive>neutral film contrast revealed significant activity in the dACC, insula, and frontal gyrus (Figure 2 and Table 1).

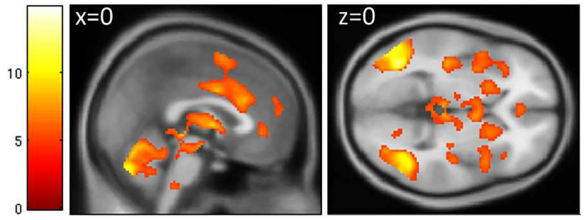

Figure 2. Activity in the contrast of aversive>neutral (FWE-corrected $p < .05$; $k \geq 5$).

Table 1. Activity pattern of aversive>neutral film-clips.

Region	Cluster Size, Voxels	z-Score	MNI coordinates, (x, y, z)
R Postcentral Gyrus	31893	Inf	30, −38, 52
L Supramarginal Gyrus		Inf	−50, −28, 34
R Occipital Lobe		Inf	26, −76, 34
R Precentral Gyrus	1501	Inf	50, 4, 38
		Inf	28, −10, 54
R Inferior Frontal Gyrus		7.83	46, 6, 26
R Cingulate	200	7.15	14, −24, 40
L ACC	212	6.61	−6, 50, 12
		6.16	−4, 52, 24
R ACC	113	6.26	0, 40, −2
Brainstem	67	5.61	0, −36, −48
L Middle Frontal Gyrus	65	5.29	−26, 44, 28
L Insula	6	5.19	−36, −4, 14
R Inferior Frontal Gyrus	5	5.05	26, 30, −12
L Middle Frontal Gyrus	15	5.05	−34, 36, 30
R Middle Frontal Gyrus	6	4.95	32, 50, 26

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite; ACC = anterior cingulate cortex.
The reverse (neutral>aversive) contrast revealed an occipital-frontal activation pattern (see Table 2).

The pain>no-pain contrast revealed activity in the dACC, anterior and posterior insula, and frontal gyrus (Figure 3 and Table 3).

The no-pain>pain contrast revealed a fronto-temporal activation pattern amongst VMPFC (see Figure 4 and Table 4).

Interaction analysis showed higher activity in the pain>no-pain contrast during aversive vs. neutral film clips in precuneus und posterior insula (Table 5; Figure 3 bar chart). The reverse interaction (pain>no-pain during neutral>aversive) revealed supramarginal gyrus activity (see Table 6).

Conjunction analysis (pain>no-pain & aversive>-neutral) revealed activity in the bilateral AI (Figure 5, left) and dACC (Figure 5, right; Table 7). These effects were mainly driven by enhanced activation in the

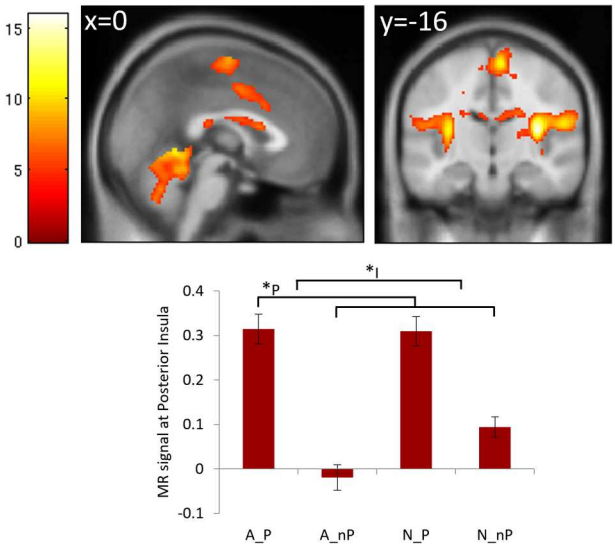

Figure 3. Pain>no-pain (FWE-corrected $p < .05$; $k \geq 5$). Parameter estimates of the posterior insula (averaged across voxels within region of interest) during all conditions (A_P = aversive pain, A_nP = aversive no-pain, N_P = neutral pain, N_nP = neutral no-pain, *P denotes significant effect of pain>no-pain, *I denotes significant interaction).

Table 2. Activity pattern of neutral>aversive film-clips.

Region	Cluster Size, Voxels	z Score	MNI coordinates, (x, y, z)
R Occipital Lobe	511	Inf	24, −94, −2
		7.08	10, −90, 22
		6.48	12, −96, 8
L Occipital Lobe	199	Inf	−26, −94, −6
		5.91	−6, −98, 10
R Middle Frontal Gyrus	187	6.62	36, 52, 0
R Posterior Insula	62	6.51	36, −16, 16
L Posterior Insula	40	6.13	−34, −18, 16
R Precuneus	78	5.99	18, −54, 20
L Middle Frontal Gyrus	67	5.89	−38, 50, −2
R Parahippocampal Gyrus	28	5.77	30, −40, −8
L Occipital Lobe	17	5.24	−6, −90, −4
R Angular Gyrus	44	5.02	38, −62, 42
L Precentral Gyrus	11	4.99	−30, −22, 54

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite.

Table 3. Activity pattern of pain>no-pain.

Region	Cluster Size, Voxels	z Score	MNI coordinates, (x, y, z)
R Posterior Insula	7128	Inf	34, −16, 14
R Insula		Inf	50, 0, 8
R Anterior Insula		Inf	36, 6, 10
R Postcentral Gyrus	2234	Inf	18, −42, 70
R Supplementary Motor Area		Inf	6, −14, 66
dACC		Inf	6, 0, 44
L Cerebellum	1369	Inf	0, −52, −4
		Inf	−22, −36, −28
		Inf	−6, −44, −18
L Postcentral Gyrus	244	7.71	−18, −40, 70
L Precentral Gyrus		5.66	−16, −28, 66
		5.37	−16, −22, 58
L Hippocampus	86	6.19	−32, −40, 2
		5.65	−36, −36, −6
L Cerebellum	34	5.34	−22, −66, −22
L Cerebellum	5	5.12	−32, −50, −30

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite; ACC = anterior cingulate cortex.

three aversive conditions (A_P, A_nP, N_P) and weak activation in the N_nP condition (see bar charts in Figure 5).

Table 4. Activity pattern of no-pain>pain.

Region	Cluster Size, Voxels	z Score	MNI coordinates, (x, y, z)
R Precentral Gyrus	1313	Inf	38,−20,50
		7.75	46,−18,58
		7.42	48,−16,48
VMPFC	838	Inf	−6,32,−14
		Inf	6,40,−16
		7.76	−12,26,−12
L Precentral Gyrus	686	7.30	−42,−24,62
L Postcentral Gyrus		6.54	−36,−36,52
L Postcentral Gyrus		6.49	−50,−16,48
R Fusiform Gyrus	126	6.64	30,−32,−20
		5.32	38,−48,−20
L Superior Frontal Gyrus	69	6.10	−24,−10,52
R Occipital Lobe	207	5.98	28,−74,36
R Middle Temporal Gyrus	154	5.72	62,−8,−18
		5.54	54,−6,−20
		5.28	52,−16,−16
R Precentral Gyrus	49	5.68	26,−8,54
L Middle Temporal Gyrus	95	5.60	−56,−16,−14
		5.23	−52,−6,−22
L Fusiform Gyrus	57	5.49	−28,−36,−18
L Occipital Lobe	14	5.23	−20,−82,38
R Parahippocampal Gyrus	11	5.01	20,−10,−22
		4.90	26,−16,−22
L Superior Frontal Gyrus	7	4.99	−6,60,22
L Parahippocampal Gyrus	6	4.88	−26,−18,−22

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite; VMPFC = ventromedial prefrontal cortex.

Table 5. Interaction 1: higher pain>no-pain activity during aversive compared to neutral film-clips.

Region	Cluster Size, Voxels	z-Score	MNI coordinates, (x, y, z)
R Precuneus	44	5.41	4,−60,24
R Precuneus	8	4.92	6,−60,52
L Posterior Insula	6	4.87	−36,−18,20

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite.

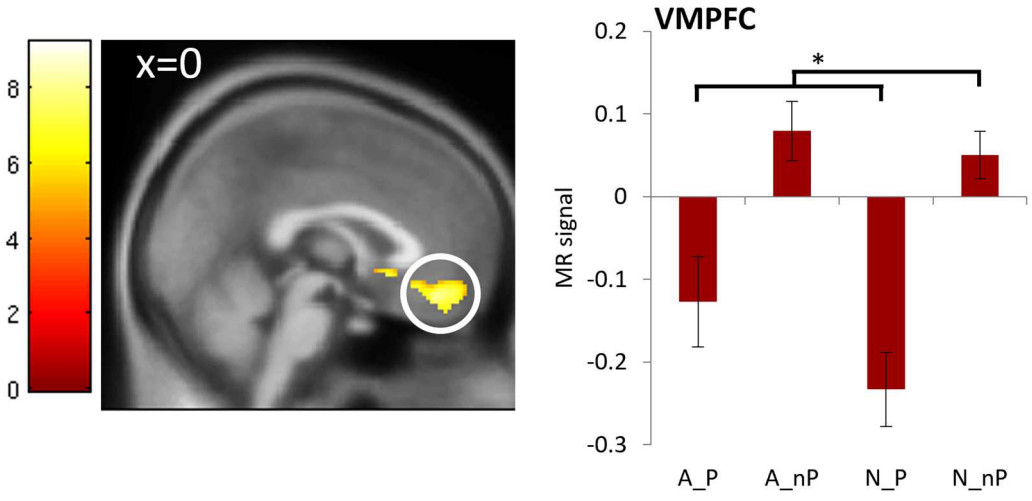

Figure 4. Activity in the contrast of no-pain>pain at FWE-corrected $p < .05$; $k \geq 5$. Parameter estimates of the ventromedial prefrontal cortex (VMPFC; averaged across voxels within region of interest) during all conditions (A_P = aversive pain, A_nP = aversive no-pain, N_P = neutral pain, N_nP = neutral no-pain, MR = magnetic resonance, * denotes significant effect of no-pain>pain).

Table 6. Interaction 2: higher pain>no-pain activity during neutral compared to aversive film-clips.

Region	Cluster Size, Voxels	z-Score	MNI coordinates, (x, y, z)
L Supramarginal Gyrus	256	6.71	−56,−24,34
		6.26	−60,−22,24

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left.

3.3. Daily life intrusions

Over the 7 days after the fMRI experiment, participants reported on average 5.25 ($SD = 7.33$) spontaneously occurring audiovisual and 1.46 ($SD = 2.22$) pain intrusions during daily life.

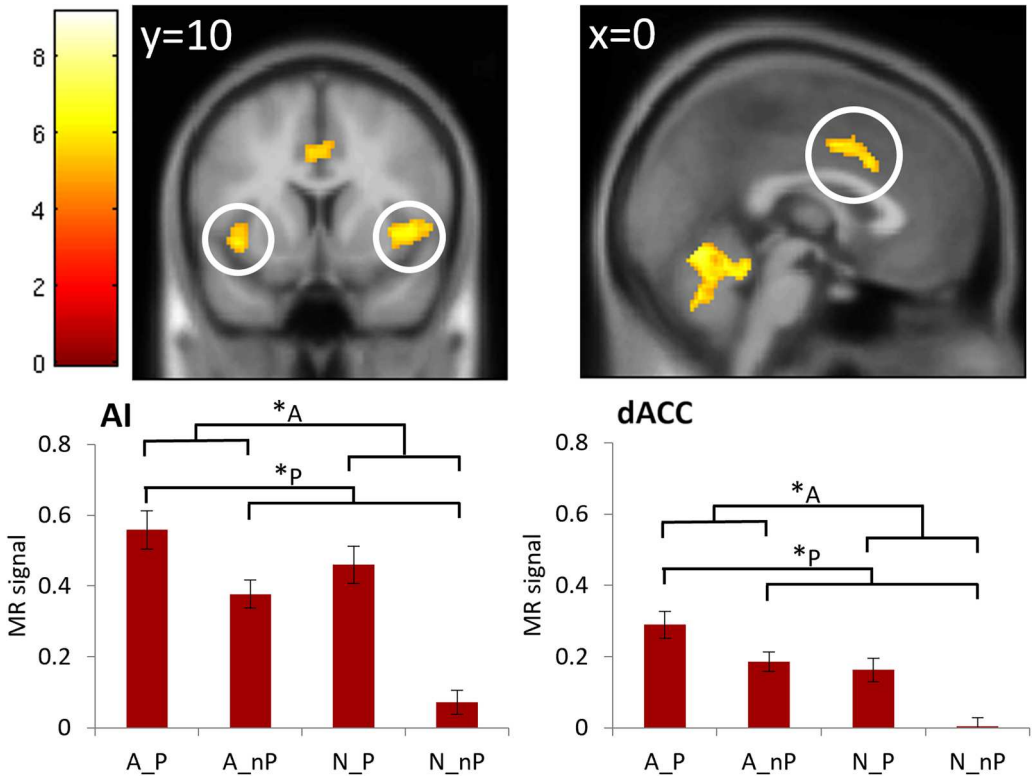

Figure 5. Bilateral anterior insula and dACC activity in both pain- and aversive-film processing revealed by conjunction analysis (pain>no-pain & aversive>neutral; FWE-corrected $p < .05$; $k \geq 5$). Parameter estimates averaged within bilateral AI and dACC mask; AI, anterior insula; dACC, dorsal anterior cingulate cortex; A_P = aversive pain, A_nP = aversive no-pain, N_P = neutral pain, N_nP = neutral no-pain; MR = magnetic resonance, *A denotes significant effect of aversive>neutral, *P denotes significant effect of pain>no-pain.

Table 7. Results of the conjunction analysis pain>no-pain & aversive>neutral.

Region	Cluster Size, Voxels	z-Score	MNI coordinates, (x, y, z)
L Postcentral Gyrus	299	Inf	−54, −28, 22
		6.53	−62, −20, 26
		6.35	−56, −16, 18
R Postcentral Gyrus	394	Inf	56, −26, 24
		7.01	50, −30, 28
Cerebellum	541	6.78	−2, −68, −12
		6.23	0, −54, −18
		6.18	2, −44, −20
L Insula	31	6.26	−38, −8, −4
R Anterior Insula	223	6.23	44, 10, 0
		5.92	36, 8, −2
L Anterior Insula	202	6.13	−46, 6, 2
		4.71	−36, 12, 4
dACC	236	5.93	0, 0, 40
		5.92	2, 16, 34
R Insula	29	5.91	38, −14, −4
		5.15	38, −4, −8
L Cerebellum	31	5.34	−22, −66, −22
L Cerebellum	5	5.12	−32, −50, −30
R Thalamus	8	5.04	20, −16, 12

Note. FWE-corrected $p < .05$; $k \geq 5$; L = left; R = right; Inf = infinite; ACC = anterior cingulate cortex.

3.4. Do neural responses to analogue-trauma predict intrusion formation?

Regression coefficients and 89%CIs of all respective models are reported in Table 8.

3.4.1. Anterior insula

Analyses revealed that higher AI activity in the aversive>neutral contrast predicted higher audiovisual intrusion probability (lower absence) over days (b = −0.13, 89%CI = [−0.25, −0.01]; Figure 6A).

Our data indicate no effect of AI aversive>neutral activity on audiovisual intrusion frequency for average levels of lifetime adversity (b = 0.08, 89%CI = [−0.01, 0.17]), yet higher AI aversive>neutral activity predicted higher audiovisual intrusion frequency in participants with high lifetime adversity (b = 0.30, 89%CI = [0.17, 0.43]; Figure 7A).

Lower AI activity in the pain>no-pain contrast predicted higher pain intrusion probability (lower

Table 8. Bayesian multilevel regression models predicting intrusions by anterior insula (AI), dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (VMPFC), and hippocampus activity in the contrasts of interest (TLEQ, Traumatic Life Events Questionnaire; significant results are marked in bold).

	(A) Hurdle (probability of intrusion absence)		(B) Lognormal (intrusion frequency)	
	b	89%CI	*b*	89%CI
AI				
I: Audiovisual Intrusions				
Aversive>Neutral	−0.16	[−0.55, 0.22]	0.08	[−0.01, 0.17]
Aversive>Neutral x Day	**−0.13**	**[−0.25, −0.01]**	0.00	[−0.03, 0.03]
Aversive>Neutral x TLEQ	−0.24	[−0.88, 0.37]	**0.30**	**[0.17, 0.43]**
Aversive>Neutral x TLEQ x Day	−0.09	[−0.28, 0.09]	−0.01	[−0.05, 0.03]
II: Pain Intrusions				
Pain>No-pain	**0.49**	**[0.01, 0.95]**	−0.10	[−0.22, 0.02]
Pain>No-pain x Day	−0.05	[−0.19. 0.08]	−0.00	[−0.07, 0.07]
Pain>No-pain x TLEQ	**0.94**	**[0.32, 1.67]**	0.03	[−0.04, 0.09]
Pain>No-pain x TLEQ x Day	−0.17	[−0.38, 0.01]	0.00	[−0.03, 0.03]
dACC				
I: Audiovisual Intrusions				
Aversive>Neutral	−0.01	[−0.39, 0.37]	0.06	[−0.04, 0.15]
Aversive>Neutral x Day	**−0.14**	**[−0.25, −0.03]**	−0.00	[−0.04, 0.03]
Aversive>Neutral x TLEQ	−0.18	[−0.58, 0.22]	**0.12**	**[0.03, 0.21]**
Aversive>Neutral x TLEQ x Day	0.02	[−0.09, 0.13]	−0.01	[−0.04, 0.01]
II: Pain Intrusions				
Pain>No-pain	0.17	[−0.32, 0.64]	−0.08	[−0.22, 0.05]
Pain>No-pain x Day	−0.07	[−0.23, 0.10]	0.00	[−0.07, 0.07]
Pain>No-pain x TLEQ	**0.72**	**[0.23, 1.31]**	0.02	[−0.03, 0.07]
Pain>No-pain x TLEQ x Day	−0.12	[−0.28, 0.02]	0.00	[−0.03, 0.03]
VMPFC				
I: Audiovisual Intrusions				
Aversive>Neutral	0.32	[−0.08, 0.72]	**−0.15**	**[−0.26, −0.04]**
Aversive>Neutral x Day	−0.01	[−0.13, 0.11]	0.00	[−0.04, 0.04]
Aversive>Neutral x TLEQ	−0.14	[−0.38, 0.08]	0.03	[−0.03, 0.08]
Aversive>Neutral x TLEQ x Day	0.03	[−0.04, 0.10]	−0.01	[−0.03, 0.01]
II: Pain Intrusions				
Pain>No-pain	0.12	[−0.37, 0.60]	**−0.14**	**[−0.27, −0.01]**
Pain>No-pain x Day	**0.18**	**[0.02, 0.35]**	0.02	[−0.04, 0.09]
Pain>No-pain x TLEQ	**1.26**	**[0.64, 1.98]**	0.00	[−0.15, 0.14]
Pain>No-pain x TLEQ x Day	0.02	[−0.24, 0.30]	−0.06	[−0.15, 0.03]
Hippocampus				
I: Audiovisual Intrusions				
Aversive>Neutral	0.24	[−0.14, 0.63]	−0.06	[−0.16, 0.04]
Aversive>Neutral x Day	−0.09	[−0.20, 0.02]	0.02	[−0.01, 0.05]
Aversive>Neutral x TLEQ	−0.24	[−0.51, 0.01]	0.05	[−0.02, 0.11]
Aversive>Neutral x TLEQ x Day	0.05	[−0.02, 0.13]	−0.01	[−0.03, 0.00]
II: Pain Intrusions				
Pain>No-pain	−0.14	[−0.64, 0.34]	−0.09	[−0.22, 0.04]
Pain>No-pain x Day	0.03	[−0.13, 0.19]	0.04	[−0.02, 0.10]
Pain>No-pain x TLEQ	**1.01**	**[0.44, 1.66]**	0.03	[−0.04, 0.10]
Pain>No-pain x TLEQ x Day	**−0.19**	**[−0.38, −0.02]**	−0.01	[−0.04, 0.02]

absence; b = 0.49, 89%CI = [0.01, 0.95]). This effect was largely driven by a tendency for higher pain intrusion probability (lower absence) with increasing AI neutral no-pain activation (b = −0.43, 89%CI = [−0.88, 0.01]), whereas other conditions showed no such relationship or a reverse pattern (aversive pain: b = 0.28, 89%CI = [−0.17, 0.74], aversive no-pain: b = −0.19, 89%CI = [−0.62, 0.23]), and neutral pain: (b = 0.35, 89%CI = [−0.10, 0.81]). Lower AI activity in the pain>no-pain contrast predicted higher pain intrusion probability (lower absence) particularly in participants with high lifetime adversity (b = 0.94, 89%CI = [0.32, 1.67]; Figure 8A).

3.4.2. dACC

Higher dACC activity in the aversive>neutral contrast predicted higher audiovisual intrusion probability (lower absence) over days (b = −0.14, 89%CI = [−0.25, −0.03]; Figure 6B). Our data indicate no effect of dACC aversive>neutral activity on audiovisual intrusion frequency for mean levels of cumulative lifetime adversity (b = 0.06, 89%CI = [−0.04, 0.15]), yet higher dACC aversive>neutral activity predicted higher audiovisual intrusion frequency in participants with high lifetime adversity (b = 0.12, 89%CI = [0.03, 0.21]; Figure 7B).

Our data showed no effect of dACC pain>no-pain activity on pain intrusion probability (absence) for mean levels of cumulative lifetime adversity (b = 0.17, 89%CI = [−0.32, 0.64]), yet lower dACC pain>no-pain activity was linked to higher pain intrusion probability (lower absence) in participants with high lifetime adversity (b = 0.72, 89%CI = [0.23, 1.31]; Figure 8B).

3.4.3. VMPFC

Lower VMPFC activity in the aversive>neutral contrast predicted higher audiovisual intrusion frequency (b = −0.15, 89%CI = [−0.26, −0.04]; Figure 9A) and

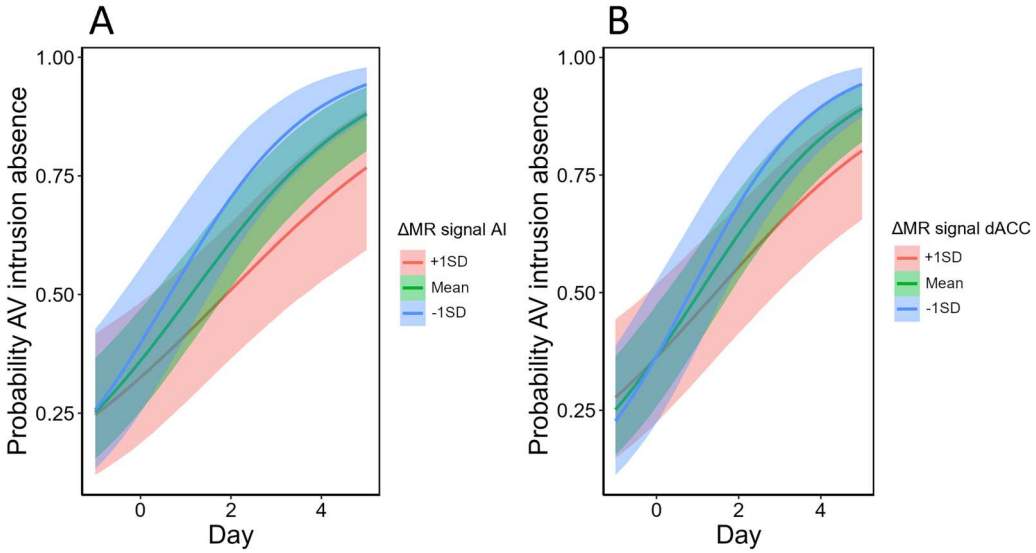

Figure 6. Participants with higher AI (A) and dACC (B) activity in the aversive>neutral contrast (red line) showed higher audiovisual (AV) intrusion probability (lower absence) over days – estimated by the Bayesian multilevel regression model's hurdle part (AI, anterior insula; dACC, dorsal anterior cingulate cortex; Day was centred on the first 24 h day after the first fMRI session, i.e. on the second experimental day).

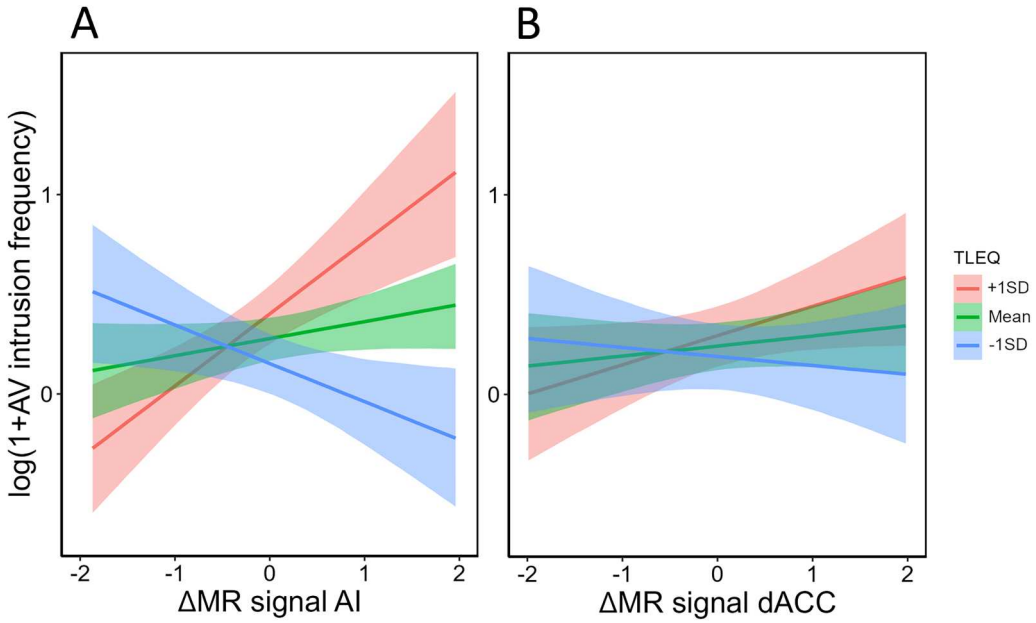

Figure 7. Aversive>neutral x TLEQ: Higher AI (A) and dACC (B) activity in the aversive>neutral contrast was linked to higher audiovisual (AV) intrusion frequency particularly in participants with high TLEQ (red line; AI, anterior insula, dACC, dorsal anterior cingulate cortex; TLEQ, Traumatic Life Events Questionnaire).

lower VMPFC activity in the pain>no-pain contrast predicted higher pain intrusion frequency (b = −0.14, 89%CI = [−0.27, −0.01]; Figure 9B). Moreover, lower VMPFC activation in the pain>no-pain contrast predicted higher pain intrusion probability (lower absence) over days (b = 0.18, 89%CI = [0.02, 0.35]). There was no effect of VMPFC pain>no-pain activity on pain intrusion probability (absence) for mean levels of cumulative lifetime adversity (b = 0.12, 89%CI = [−0.37, 0.60]), yet lower VMPFC pain>no-pain activity was linked to higher pain intrusion probability (lower absence) in participants with high lifetime adversity (b = 1.26, 89%CI = [0.64, 1.98]; Figure 8C).

3.4.4. Hippocampus

Analyses revealed no significant effects of hippocampus activity on audiovisual intrusions (Table 8). There was no effect of hippocampus pain>no-pain activity on pain intrusion probability (lower absence) for mean levels of cumulative lifetime adversity (b = −0.14, 89%CI = [−0.64, 0.34]), yet lower hippocampus pain>no-pain activity was linked to higher pain intrusion probability (lower absence) in participants with

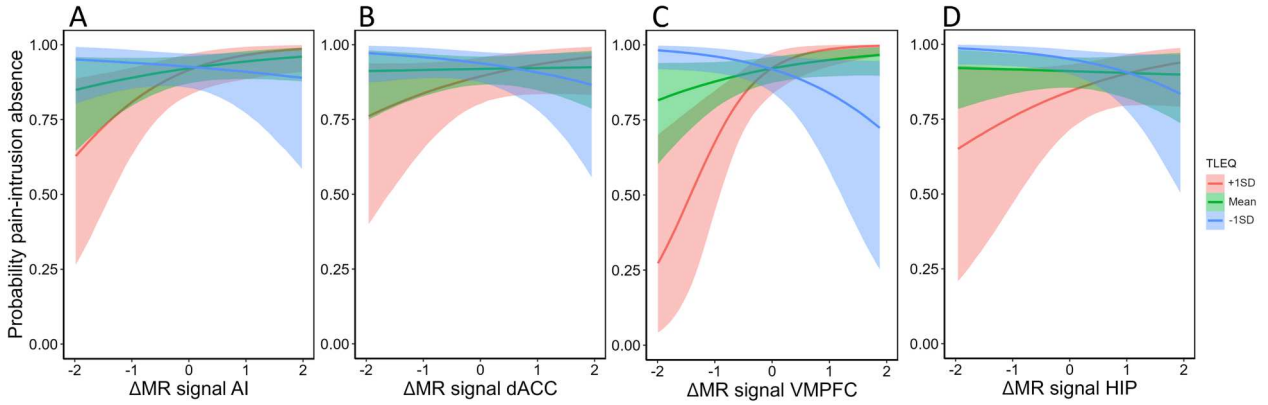

Figure 8. Pain>no-pain x TLEQ: Lower AI (A), dACC (B), VMPFC (C), and hippocampus (D) activity in the pain>no-pain contrast was linked to higher pain intrusion probability (lower absence) particularly in participants with high TLEQ (red line; AI, anterior insula; dACC, dorsal anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex; HIP, hippocampus; TLEQ, Traumatic Life Events Questionnaire).

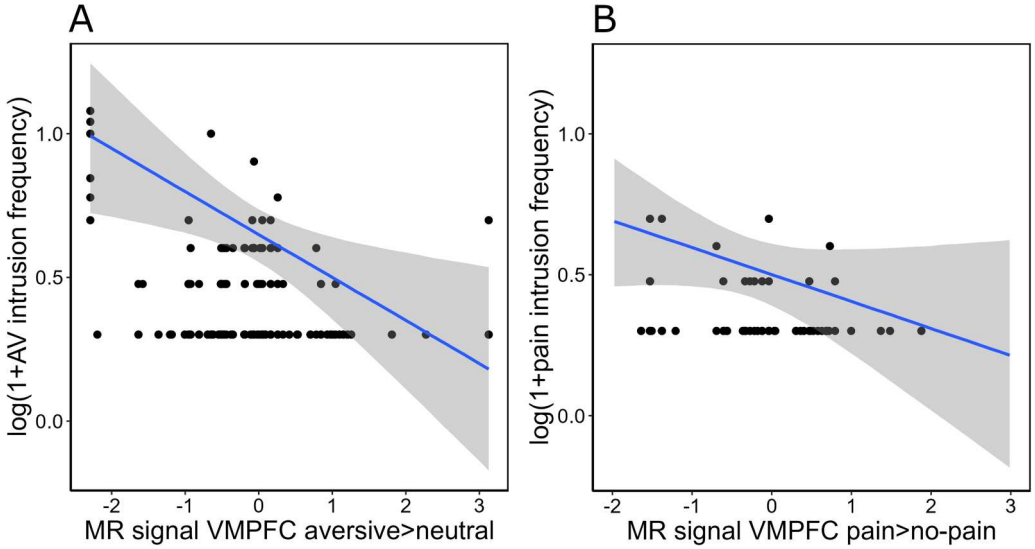

Figure 9. (A) Lower VMPFC activity in the aversive>neutral contrast predicted higher audiovisual intrusion frequency – estimated by the model's lognormal part. (B) Lower VMPFC activity in the pain>no-pain contrast predicted higher pain intrusion frequency – estimated by the model's lognormal part (VMPFC, ventromedial prefrontal cortex; AV = audiovisual; brain activity was centred to its respective mean).

high lifetime adversity (b = 1.01, 89%CI = [0.44, 1.66]; Figure 8D), which was modulated by day (b = −0.19, 89%CI = [−0.38, −0.02]).

3.5. Analyses for the influence of lifetime adversity on neural activity and intrusion formation

First, the TLEQ–sum score had no significant effect on film processing (aversive>neutral) and pain processing (pain>no-pain) in all ROIs (TLEQ-effect on film processing in AI (b = −0.06, 89%CI = [−0.20, 0.07]), dACC (b = −0.02, 89%CI = [−0.11, 0.07]), VMPFC (b = −0.01, 89%CI = [−0.11, 0.09]), and Hippocampus (b = 0.03, 89%CI = [−0.04, 0.11]); TLEQ-effect on pain processing in AI (b = −0.17, 89%CI = [−0.35, 0.01]), dACC (b = −0.05, 89%CI = [−0.16, 0.06]), VMPFC (b = 0.02, 89%CI = [−0.12, 0.16]), and Hippocampus (b = 0.06, 89%CI = [−0.03, 0.15])). Second, the TLEQ–sum score had no effect on audiovisual intrusion absence (b = −1.55, 89%CI = [−4.24, 0.18]) and audiovisual intrusion frequency (b = 0.11, 89%CI = [−0.08, 0.29]). Moreover, the TLEQ–sum score had no effect on pain intrusion absence (b = −0.65. 89%CI = [−3.43, 1.26]) and pain intrusion frequency (b = 0.19, 89%CI = [−0.00, 0.38]).

4. Discussion

While pain is common during traumatic events, the processing of pain during trauma is poorly understood. Combining aversive 'trauma' films and painful stimulation, this study demonstrates that both aversive films and pain stimulation relative to the neutral no-pain control condition activated core brain regions of threat processing like AI and dACC. In addition, no-

pain compared to pain revealed a fronto-parietal activation pattern involving VMPFC. Higher AI and dACC activity predicted higher audiovisual intrusion probability over days. Particularly in participants with high lifetime adversity, higher AI and dACC activity was associated with a higher frequency of audiovisual intrusions. Conversely, lower AI, dACC, VMPFC, and hippocampal activity predicted higher probability of pain intrusions, particularly in high lifetime adversity participants. Lower VMPFC activity predicted both higher audiovisual- and pain intrusion frequency.

4.1. Neural responses to analogue trauma

Enhanced valence and pain ratings during aversive compared to neutral no-pain conditions in combination with activated core regions within the threat processing network (Mobbs et al., 2009) provide further support for the validity of the trauma-film paradigm as a PTSD analogue (James et al., 2016) and extend it to the study of traumatic pain processing. Interestingly, aversive film-clips without painful stimulation were rated as painful to some extent, which could be related to mirroring of another person's pain experience (Lamm et al., 2011; Lamm & Singer, 2010; Singer et al., 2004).

Analyses revealing heightened activations in the dACC and AI in the aversive>neutral as well as in the pain>no-pain contrasts validate previous findings proposing AI as well as dACC to be sensitive to analogue trauma (Miedl et al., 2018; Miedl et al., 2020; Rattel, Miedl, et al., 2019). Yet, these regions were likewise activated by a neutral film in a pain context, pointing towards an activation of dACC and AI during both aversive film-clips and painful stimulation. Moreover, the overall heightened dACC and AI activation during both aversive and pain conditions might reflect central autonomic – interoceptive network activity (Fullana et al., 2018). In this way, the AI might be involved in integrating cognitive, affective, and physical states being represented in the dACC for initiating homeostatic autonomic and behavioural responses, similar to AI involvement in social affective state integration (Miedl et al., 2016). Both dACC and AI have important roles in the detection of salient stimuli as core nodes of the saliency network (Seeley et al., 2007) and in emotional reactivity (Etkin et al., 2015). Regarding emotional reactivity, dACC and AI seem to be particularly important in eliciting negative emotional states and threat-related anticipatory anxiety (Etkin et al., 2011). Therefore, the findings of the present study support that AI and dACC are highly involved in the processing of trauma-films and pain, which could point to aversive affective state – pain integration and anticipatory anxiety.

Neutral no-pain compared to pain revealed a fronto-parietal activation pattern comprising the VMPFC, which is in agreement with the general deactivation of VMPFC during pain processing (Wager et al., 2013). Additive effects of pain stimulation on top of aversive film-viewing could only be observed in precuneus and posterior insula (see Table 5), which is reflected by stronger pain vs. no-pain discrimination during aversive vs. neutral conditions. Relatedly, on a neural level a non-significant difference in AI and dACC during aversive vs. neutral films in the context of pain reflects that during pain the (aversive film) context had no additive effect, which is also reflected by similar pain and valence rating patterns during aversive film and/or pain conditions. One reason could be that participants who experience painful stimulation while watching aversive films might be distracted by their content similar to virtual reality distraction leading to pain relief (Indovina et al., 2018), which could not be related to pure pain perception because of similar posterior insula activity in aversive pain and neutral pain conditions. On the other hand, the present results point to 'healthy' pain processing, prioritizing potential tissue damage during pain stimulation independently of the audiovisual (aversive) context. One could speculate whether applying highly personally-relevant aversive stimuli (e.g. trauma scripts in PTSD patients) and potentially inducing enhanced levels of dissociation (Danböck et al., 2023; Schauer & Elbert, 2010) would lead to more maladaptive pain processing. Thus, the PTSD relevance of the present study might be best captured by relating brain activity of both trauma-film and pain-sensitive regions to intrusion formation.

4.2. Relation of peritraumatic processing to intrusion formation

The fact that dACC and AI were both active in the processing of traumatic and painful events provides support to further explore their relationship with intrusions – as a possible mechanism underlying the development of PTSD (Menon & Uddin, 2010). Here we put a novel focus on the effects of trauma-associated pain because pain is common during traumatic events and since PTSD and medically unexplained pain frequently co-occur. Lower pain>no-pain activity in the AI predicted a higher probability of pain intrusions. Therefore, weakened discriminatory AI central autonomic-interoceptive processing (Fullana et al., 2016) might facilitate the encoding of painful stimuli within a trauma-associated memory network. This in turn could result in stronger memory representations of the aversive stimuli, which might shift the attention to stimuli similar to the traumatic event in daily life and therefore enhance reactivating these memory representations (Brewin et al., 2010), including representations in the somatosensory modality. Therefore, sensitivity to aversive films and/

or painful stimulation and the association with pain intrusions might also point to the recruitment of this network: Poor pain vs. no-pain discrimination in the AI could have led to a broader affective state integration, to strong memory representations in response to cues, and facilitation of formation of pain intrusions (Brewin et al., 2010). This effect was partly driven by enhanced AI activity during the 'safe' neutral no-pain condition being related to higher probability of pain intrusions, which suggests exaggerated threat detection and emotional responses to not dangerous situations (Kunimatsu et al., 2020) as a vulnerability factor for pain intrusions.

Pain perception is greatly influenced by cognitive factors, affect, and valuation (Reddan & Wager, 2018). In contrast to inter-individual differences in the emotional reactivity to aversive film-viewing, the inter-individual intensity of pain application was held constant due to pre-experimental calibration, which likely resulted in less inter-individual variance in activation of brain regions related to pain processing for pain intrusion prediction. As enhanced activation in regions such as AI and dACC during painful stimulation seems to be associated with chronic pain (Kregel et al., 2015; Kuner & Flor, 2017), and pain intrusions might function as a precursor of chronic pain (Clark & Mackay, 2015; Macdonald et al., 2018), one might speculate that altered peritraumatic neural processing in the AI and dACC could be a specific risk factor for pain chronification (Ong et al., 2019).

Although the processing of pain stimuli and investigating pain intrusions in the context of trauma was a particular novel aspect of our study, we were also interested in replicating and extending previous findings regarding trauma film processing and audiovisual intrusions. Stronger AI and dACC activity in the aversive>neutral contrast revealed higher audiovisual intrusion probability over time which replicates general AI and dACC sensitivity to trauma cues being linked to intrusions in healthy women (Miedl et al., 2020; Rattel, Miedl, et al., 2019). Generally, the present findings point to an involvement of heightened central autonomic–interoceptive processing (Fullana et al., 2018) in audiovisual intrusion formation and are in agreement with previous studies linking networks around the dACC to analogue intrusions (Battaglini et al., 2016; Bourne et al., 2013; Clark et al., 2016).

Decreased VMPFC activity during aversive and pain conditions predicting higher audiovisual and pain intrusion frequency could be related to unsuccessful emotion regulation (Etkin et al., 2011), which also plays an important role in PTSD (Etkin & Wager, 2007). In addition, the increased likelihood of pain intrusions over days in participants with low VMPFC pain vs. no pain activity is consistent with the role of the VMPFC in pain modulation (Ong et al., 2019). Consequently, VMPFC hypoactivity during aversive conditions correlating with PTSD symptom severity (Fragkaki et al., 2016; Pitman et al., 2012; Rauch et al., 2006) fits to a general (audiovisual and pain) – VMPFC intrusion sensitivity: individual differences in the capability to downregulate threat responses via VMPFC may be important in the case of intrusion formation and their elicitation. The hippocampus showed no effects on audiovisual intrusions, demonstrating that previously reported hippocampal hyperactivity during perceptual processing of arousing autobiographical memories (Moscovitch et al., 2016) and reported sensitivity for encoding of negative images in participants with intrusions (Battaglini et al., 2016) cannot be directly linked to audiovisual intrusion formation.

The finding that both enhanced AI and dACC activity was associated with both a higher intrusion persistence over days and the frequency of audiovisual intrusions particularly in participants with high lifetime adversity replicates previous results by Rattel, Miedl et al. (2019). It also supports the notion of exaggerated fear processing as a vulnerability factor in PTSD (Rauch et al., 2006). For pain intrusions, results showed a different pattern: lower AI, dACC, VMPFC, and hippocampal activity were associated with a higher probability of pain intrusions primarily in participants with high lifetime adversity. This may be due to poor pain/no-pain discrimination in central regions involved in linking interoceptive and emotional or cognitive states for further integration and generation of regulatory signals (Chen et al., 2021), which – particularly in combination with high lifetime adversity – may facilitate the generation of pain intrusions. It may also suggest a different neural mechanism for the formation of audiovisual and pain intrusions in individuals with high lifetime adversity, where variance in peritraumatic cognitive processing (e.g. Rattel et al., 2022) between audiovisual and pain modality may play an important role. Taken together, the present findings confirm the moderating role of cumulative lifetime adversity on the relationship between peritraumatic neural processing during analogue trauma and intrusion formation (Breslau et al., 1999). Subanalyses of effects of specific types of lifetime adversity were not conducted due to the heterogeneity of adversities over participants (see Supplement Table S1 and Figure S1).

4.3. Limitations

The present sample only consisted of female participants. Since studies suggest gender specific differences in responding to aversive films and pain (Bartley & Fillingim, 2013; Rattel, Wegerer, et al., 2019; Wilhelm et al., 2017), results cannot be generalized to men without further investigations assessing a mixed

sample. Moreover, results from analogue studies do not necessarily generalize to clinical populations.

4.4. Conclusion

Processing of both trauma-films and pain involves the AI and dACC. Moreover, heightened AI and dACC activity during aversive conditions especially in combination with high lifetime adversity may be important processes for the development of audiovisual intrusions. Conversely, the formation of pain intrusions might be driven by weak discrimination between painful and non-painful conditions in AI, dACC, VMPFC, and hippocampus, particularly in participants with high lifetime adversity. Weak regulatory VMPFC activity seems to be a general vulnerability factor for both audiovisual and pain intrusion formation. These results may shed light on the contribution of peritraumatic cognitive and affective neural processing during trauma and how these factors may lead to PTSD symptoms and medically unexplained pain.

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Data availability statement

As participants did not provide consent to make raw data publicly available, data are, in conjunction with an appropriate data sharing agreement, available on request from SFM.

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