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# The differential effect of trigeminal vs. peripheral pain stimulation on visual processing and memory encoding is influenced by pain-related fear

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ABSTRACT

Compared to peripheral pain, trigeminal pain elicits higher levels of fear, which is assumed to enhance the interruptive effects of pain on concomitant cognitive processes. In this fMRI study we examined the behavioral and neural effects of trigeminal (forehead) and peripheral (hand) pain on visual processing and memory encoding. Cerebral activity was measured in 23 healthy subjects performing a visual categorization task that was immediately followed by a surprise recognition task. During the categorization task subjects received concomitant noxious electrical stimulation on the forehead or hand. Our data show that fear ratings were significantly higher for trigeminal pain. Categorization and recognition performance did not differ between pictures that were presented with trigeminal and peripheral pain. However, object categorization in the presence of trigeminal pain was associated with stronger activity in task-relevant visual areas (lateral occipital complex, LOC), memory encoding areas (hippocampus and parahippocampus) and areas implicated in emotional processing (amygdala) compared to peripheral pain. Further, individual differences in neural activation between the trigeminal and the peripheral condition were positively related to differences in fear ratings between both conditions. Functional connectivity between amygdala and LOC was increased during trigeminal compared to peripheral painful stimulation. Fear-driven compensatory resource activation seems to be enhanced for trigeminal stimuli, presumably due to their exceptional biological relevance.



## Introduction

Nociceptive signals from the head and facial area are signs of potential danger to essential vital functions. Facial pain has been proposed to have a higher biological relevance than pain located in the periphery and might be prioritized over pain in other body parts. Several lines of evidence support this prioritization hypothesis. We have recently shown increased sensitization for noxious heat stimuli applied to the face as compared to pain stimuli applied to the hand (Schmidt et al., 2015). Interestingly, pain-related fear was higher for trigeminal pain as compared to pain on the extremities despite comparable pain intensity ratings. Moreover, noxious facial stimulation leads to faster fear conditioning compared to noxious tibial stimulation when used as an unconditioned stimulus (Meier et al., 2014) and painful stimuli applied to the hand positioned near compared to further away from the face lead to enhanced defensive hand-blink-reflexes (Sambo et al., 2012).

Due to its biological warning function pain captures attention and interrupts ongoing cognitive processes. This interruptive effect of pain on cognitive processes (Eccleston and Crombez, 1999) is a well-established phenomenon induced by both acute and chronic pain states (Eccleston, 1995; Kuhajda et al., 2002; Grisart et al., 2007; Moore et al., 2012), and has been shown to affect different cognitive domains such as working memory, short-term memory and visual processing (Bingel et al., 2007; Oosterman et al., 2011; Forkmann et al., 2013). Interestingly, the interruptive function of pain is not necessarily linearly related to the intensity of pain, but depends on top–down and bottom–up factors including personality traits and expectation (Crombez et al., 1998; Van Damme et al., 2004; Vancleef and Peters, 2006; Tiemann et al., 2010) as well as stimulus characteristics (Crombez et al., 1994; Buhle and Wager, 2010; Sinke et al., 2015).

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In this study we aimed at exploring whether the interruptive function of pain differs between the head and facial region and peripheral body parts. To this end, we combined a well-established visual encoding and recognition paradigm known to be sensitive to the interruptive effects of pain (Forkmann et al., 2013, 2015; Sinke et al., 2016) with noxious electrical stimulation of comparable subjective intensity to the forehead or the hand. The effects of trigeminal and peripheral pain (in the following referred to as face pain and hand pain) on visual processing, memory encoding and retrieval were assessed on the behavioral level with an object categorization task and a surprise recognition task. Neural effects were tested using fMRI. Given the crucial biological relevance and higher pain-related fear of face pain, we assumed a larger interruptive effect of pain when applied to the face compared to stimuli applied to the hand. Specifically, we predicted lower visual categorization and memory performance when the noxious stimulation is applied to the face as compared to the hand. On the neural level, we expected reduced activation in visual and memory-related areas such as hippocampus and parahippocampus (Forkmann et al., 2013) during face as compared to hand pain. Given the higher threat value of facial pain compared to pain on the extremities (Meier et al., 2014; Schmidt et al., 2015), we predicted increased neural activation in brain areas involved in emotional and fear processing such as the amygdala (Bishop et al., 2004; Sehlmeyer et al., 2009) during face pain. Finally we aimed at exploring pain- and task-induced connectivity changes between pain-related, task-related and fear-related brain areas.

## Methods

In the following the terms *face pain* and *hand pain* refer to the pain stimulation site, i.e. the forehead and the back of the hand.

### *Subjects*

Imaging and behavioral data were acquired in 30 healthy subjects. Behavioral data analyses comprised data from 26 subjects (all right-handed, 11 male; age in years: 27.4 ± 4.2 (M ± SD)). Four subjects had to be excluded due to the following reasons: $n = 2$ reported no painful sensation during the task, $n = 1$ due to technical failure of the electrical stimulator and $n = 1$ due to a dislocated electrode. Three additional subjects had to be excluded from fMRI analyses due to technical failure of the scanner. Therefore, fMRI data analysis comprised data from 23 subjects (all right-handed, 11 male; age in years: 27.8 ± 4.2 (M ± SD)). All subjects reported normal or corrected-to-normal eyesight, normal hearing and no known history of neurological or psychiatric and pain-related diseases. All subjects gave written informed consent to participate and were free to withdraw from the study at any time. The study was conducted in accordance with the declaration of Helsinki and had been approved by the local ethics committee in Essen, Germany. The subjects received a small monetary compensation for their study participation.

### *Experimental paradigm*

The experimental paradigm used here is a modified version of a visual encoding paradigm reported previously (Forkmann et al., 2013). The study was conducted in 2 days. On day 1, the subjects underwent the assessment of pain thresholds on both stimulation sites and a calibration procedure in order to determine individually calibrated electrical pain stimuli to be applied on the hand and the face. Painful hand and face stimulation was adjusted separately to yield comparable pain intensity levels of 70 on a 0–100 visual analog scale (VAS, anchors 0 = "not painful at all" and 100 = "unbearably painful"). The subjects performed a practice run of the visual encoding task. All relevant behavioral and imaging data were acquired on the second day of the study (1–5 days later). The main fMRI experiment comprised (1) the simultaneous presentation of visual and painful stimuli (visual categorization task, memory encoding) and (2) a subsequent surprise recognition task to investigate differential effects of painful face and hand stimulation on memory performance. Both tasks were performed inside the 3T MR scanner.

### *Experimental procedures*

#### *Day 1*

On day 1, the subjects filled in questionnaires assessing pain-related psychological processing [Pain Anxiety Symptom Scale (PASS); Pain Catastrophizing Scale (PCS); Pain Vigilance and Awareness Questionnaire (PVAQ)], anxiety and depression [ADS-K; State Trait Anxiety Inventory (STAI), Trait Scale]. For details see the section on "Psychological questionnaires". The participants were then familiarized with the electrical stimuli and underwent calibration procedures with different stimulation intensities that had to be rated for subjective pain intensity on a VAS. First, we assessed electrical pain thresholds separately for both sites of stimulus application [(1) back of the left hand, approximately 2 cm away from the knuckle of the index finger, (2) left side of the forehead, approximately 1 cm above the outer end of the eyebrow]. Thresholds were obtained using single-pulse stimuli with 0.5 ms duration and by increasing the current by 0.01 mA between consecutive stimuli starting at 0 mA (ascending method of limits) (Gescheider, 1997). The upper limit was set to 15 mA to avoid tissue damage. The participants verbally indicated when their perception changed from a tingling to a painful sensation. This procedure was repeated three times for each stimulation site and the mean mA was defined as the site-specific pain threshold. Subsequently, the subjects underwent a pain calibration procedure to determine the stimulation intensity corresponding to a level of 70 on a 0–100 VAS. To this end, trains of stimuli with 2.5 s duration and of varying intensity levels around their individual pain threshold were applied. After each stimulus, the participants rated their subjective pain intensity on a VAS that was presented on a computer screen. The stimulation intensity that corresponded to a VAS level of 70 was chosen to be applied during the experiment. Pain threshold determination and calibration of the stimulation intensity were performed separately for hand and face in counterbalanced order.

#### *Day 2*

On day 2 the fMRI experiment was conducted. Before performing the task inside the scanner, the subjects completed the state scale of the STAI. Immediately before scanning, the subjects performed a number of pretests, including a recalibration of pain stimuli and the assessment of fear and expectation ratings. During recalibration, 5 pain stimuli were applied to the subjects' hand and forehead to test whether stimulus intensities determined on day 1 still yielded intensity levels of approximately 70 when the subjects were lying in the MR scanner. In case the intensity ratings differed largely from 70, stimulation intensity was adjusted. Prior to the main task, the subjects were asked to rate their fear regarding the upcoming stimulation separately for both body sites (presentation of the word "hand" or "face" before the appearance of the VAS) on two 0–100 VAS ("Please indicate how fearful you are about the upcoming stimulation.", VAS anchors: 0 = "not fearful at all" and 100 = "extremely fearful"). Further, the participants were asked to rate their expectation regarding (1) the effect of pain on task performance and (2) the effect of task performance on pain perception on a VAS ((1) "Please indicate how the painful stimulation will influence your task performance.", VAS anchors: −50 = "strong performance decrease" and 50 = "strong performance increase"; (2) "Please indicate how performing the task will influence your pain perception.", VAS anchors: −50 = "decreased pain perception" and 50 = "increased pain perception").

Subsequently, the subjects performed the encoding task, which was introduced as a visual categorization task (duration ~10 min). First, all subjects performed 6 practice trials (3 of each condition). These trials

also served to ensure that, while performing the categorization task, pain intensities were still high and comparable between both stimulation sites. The test trials included 40 images of living and nonliving objects (see "Visual stimuli" section). All pictures were presented with concurrent painful stimulation either on the (1) forehead ('face pictures') or the (2) back of the hand ('hand pictures'). Thus, each condition comprised 20 trials (10 living, 10 nonliving objects) that were presented in a pseudorandomized order with no more than three consecutive pain stimuli of the same type. The trial structure was as follows: presentation of a white fixation cross (variable duration of 5–8 s), image and concomitant painful stimulation (2.5 s), presentation of a white fixation cross (variable duration of 3–6 s; see Fig. 1), a rating period (no time limit). The participants were asked to categorize each picture as living or nonliving by pressing one of two buttons as quickly as possible without compromising on accuracy (categorization task). Moreover, the subjects rated the pain intensity of each electrical pain stimulus using a VAS. Categorization choice, reaction times (RTs), and pain intensity ratings were recorded as behavioral outcome measures.

The categorization task was immediately followed by a surprise recognition task (duration ~12 min) in order to compare the interruptive effect of painful face and hand stimuli on object encoding. In the recognition task, all images shown in the categorization task were presented again, intermixed with the same number of images that had not been presented before. The subjects were instructed to indicate a known (old) or unknown (new) image by giving their confidence rating on a 6-point confidence scale (anchors "surely old"–"surely new"). Overall, 80 images (40 old and 40 new images) were presented for 1.5s each, followed by the confidence rating and a fixation cross of 5 s duration before the next image was shown. Confidence ratings were recorded as behavioral outcome measures. In the recognition task no painful stimulation was applied.

### *Stimuli*

The presentation of the visual stimuli, triggering of the electrical stimuli and recording of the behavioral data were performed using the software Presentation (www.neurobs.com).

### *Visual stimuli*

The visual stimuli consisted of pictures showing natural scenes with living (e.g. animals) or nonliving (e.g. cars, buildings) objects. Eighty-eight pictures with neutral valence were selected that have been used in our lab before (Forkmann et al., 2013). For the categorization task 40 images were randomly selected, 40 other pictures were chosen for the recognition task as new images and the remaining 8 pictures were used in the practice trials. Within the encoding task all images were presented with a reduced visibility of 33% to increase the difficulty of the task using a scrambling routine as described in Rose et al. (2005). Recognition task pictures were presented at full visibility. The outer edges of the pictures were smoothed (28 mm FWHM isotropic kernel) to embed the pictures into the black background. Visual stimuli were presented on a back projection screen located behind the MR scanner. The screen could be seen via a mirror that was attached to the head coil. The pictures had a visual angle of 11.6° × 8.4°.

### *Electrical pain stimuli*

Painful stimulation was applied using two electrical stimulators (Digitimer DS7A constant current stimulator, Hertfordshire, UK) and surface electrodes (Specialty Developments, Bexley, UK) with a diameter of approximately 5 mm that were attached to the skin using medical tape. We applied 82 single pulses of 0.5 ms duration with an inter pulse interval of 30 ms resulting in a train of painful stimulation with 2.5 s duration. The experimental setup required positioning the electrodes and their cabling into the center (head electrode) and close to the end rings (hand electrode) of the integrated radio-frequency (RF) body coil and thus directly into the RF transmit field used for MR excitation. Since this increases the probability of tissue damage due to currents induced by electro-magnetic wave coupling, we replaced the standard copper cables by custom-built cables that included special non-magnetic chip resistors every 6 cm along the cable as dampers. Timing parameters of the stimulation that would ensure simultaneous perception of visual and painful stimuli on both body sites were determined in a preparatory study performed in 17 healthy volunteers (data not shown). There were no differences in perception thus visual and painful stimuli were presented simultaneously. Further we assessed stimulus-induced eye blinks to both types of stimulations in this preparatory study that revealed no difference in eye blink frequency between conditions.

The ecological validity of the pain stimulus is a concern in many experimental studies, especially studies using electrical stimuli. The choice of this experimental pain model was based on two reasons: First, the visual task used in our study that allows us to test for the perception, encoding and recognition of visual objects requires the simultaneous presentation of painful stimuli and visual objects (presentation time 2.5 s) on different body parts within the same scanning session. Such flexible stimulation is most easily implemented by the use of electrical stimulation. Second, when aiming at investigating CNS responses to facial compared to other pain using fMRI, the choice of the stimulation device is limited by a number of methodological and physical constrains as the stimulation has to be performed within the head coil. Again the

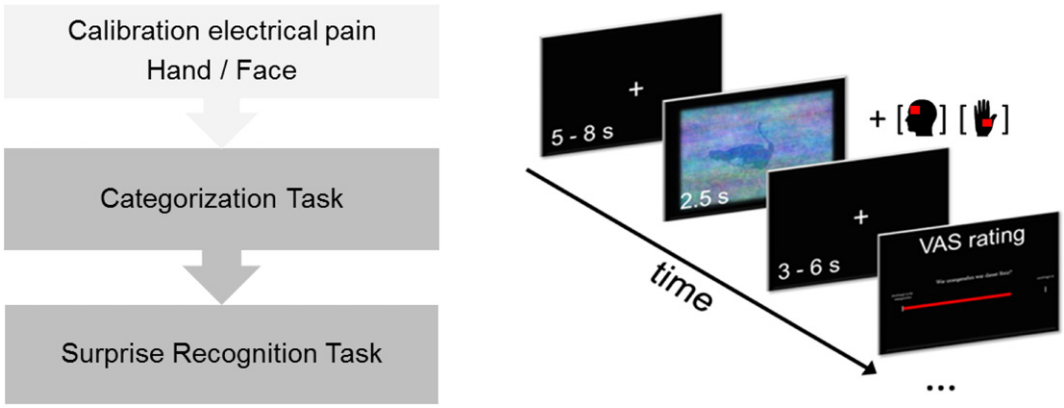


**Fig. 1.** left: Experimental protocol. Order of experimental procedures: After completing preparatory procedures, the participants performed the categorization task (encoding phase) and recognition task. Procedures colored in dark gray were conducted inside the MR scanner. Right: Categorization task. During the categorization task (encoding phase), we presented 40 images of living or nonliving objects with reduced visibility (33%) for 2.5 s each. Half of the trials were combined with painful electrical stimulation on the hand whereas the other half was paired with painful electrical stimulation in the face (duration of 2.5 s). The participants rated the pain intensity after each trial using a digital VAS.

electrical stimulation used in our study seemed best suited to meet these requirements.

*Psychological questionnaires*

The subjects completed the German versions of the questionnaires assessing anxiety, depression and pain-related psychological processing, since these variables have been shown to modulate the interruptive function of pain (Peters et al., 2002; Van Damme et al., 2004). Specifically, the participants completed the following questionnaires: (1) Pain Vigilance and Awareness Questionnaire: PVAQ (McCracken, 1997), German version (Lautenbacher et al., 2009); (2) Pain Anxiety Symptom Scale: PASS-D (McCracken et al., 1992), German version (Walter et al., 2002); (3) Pain Catastrophizing Scale: PCS (Sullivan et al., 1995), German version (Lautenbacher et al., 2009); (4) Center for Epidemiological Studies Depression Scale (Radloff, 1977), German version: ADS-K (Hautzinger and Bailer, 1993); and (5) State Trait Anxiety Inventory: STAI (Spielberger et al., 1983), German version (Laux et al., 1992). All questionnaires were analyzed following the respective manuals.

*Behavioral data*

*Analysis of behavioral data*

Behavioral data were automatically recorded and logged by the stimulation program *Presentation* (www.neurobs.com). All behavioral data analyses were conducted using SPSS version 22.0. The results with a $p < 0.05$ are considered as statistically significant. All statistical analyses were performed using two-tailed testing. The means ± standard deviation (SD) is reported, if not specified otherwise. To compare categorization performance (accuracy and RTs) between the conditions '*hand pictures*' and '*face pictures*' paired *t*-tests were performed. The mean RTs were calculated for correctly categorized images separately for both experimental conditions after excluding extreme outliers (>3 SD above mean). RTs longer than 2.5 s were not recorded. Previous studies revealed inter-individual differences in the effect of painful stimulation on RTs (Tiemann et al., 2010) and an influence of pain-related and anxiety-related personality traits on disengagement from pain (Van Damme et al., 2004). Therefore, we performed correlational analyses using Pearson's correlation coefficient with the questionnaire and behavioral data (e.g. RTs categorization task) and used Bonferroni correction for multiple comparisons.

For comparison of recognition accuracy between both experimental conditions a paired *t*-test was performed. To this end, we calculated the percentage of images classified as old (pooled across confidence levels "sure old"–"rather old" (1, 2 and 3 of confidence scales)) and new (pooled across confidence levels "sure new"–"rather new" (6, 5 and 4 of confidence scales)). The number of correct old or new classifications was divided by the number of presented pictures for each condition, separately. To account for false alarms, we calculated the discrimination index $d'$ (Stanislaw and Todorov, 1999) for both experimental conditions separately using the formula $d' = z(hit\ rate) - z(false\ alarm\ rate)$. Higher values of $d'$ indicate better discrimination, and therefore better recognition memory. The mean pain intensity ratings were calculated for both pain conditions. Differences in pain intensity ratings between painful face and hand stimulation, pain thresholds and calibrated stimulation intensities of both stimulation sites, and fear and expectation ratings were assessed using paired *t*-tests.

*Behavioral pilot study*

In preparation of the fMRI study we performed a behavioral study using the same experimental paradigm and procedures without brain imaging to test for possible differences in visual processing and encoding between conditions at the behavioral level. Categorization as well as recognition performance for pictures paired with face pain and pictures paired with hand pain was assessed in 17 healthy volunteers (all right-handed, 8 male; age in years: 25.2 ± 4.6 (M ± SD)). Data analyses were performed following the same procedures as described before (see "Analysis of behavioral data" section). Please note that the pilot study was performed on a completely different sample of healthy volunteers than the fMRI study.

*Imaging data*

*Image data acquisition*

Functional data was acquired on a 3T MR system (Siemens Magnetom, Skyra syngo MR D13) with a standard 32-channel head coil (Skyra, Siemens Healthcare, Erlangen, Germany). Functional imaging data with a total of 42 axial slices (slice thickness 2.7 mm) per volume were acquired using gradient multi-echo EPI with three echos (TE 1 13.0 ms, TE 2 28.9 ms, TE 3 44.8 ms, TR 2.89 s; flip angle 90°; field of view 224 × 224 mm). Structural images were obtained for each participant using a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE, slice thickness 1 mm; TR 2.30 s; TE 2.07 ms; flip angle 9°; field of view 256 × 256 mm).

*Image preprocessing*

Before data analysis, all imaging data were screened for scanner artifacts using the SPM toolbox ArtRepair. Image processing and statistical analysis of fMRI data were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm/). The first five volumes were removed to allow for T1 saturation. Preprocessing included slice timing and realignment to the first volume. To correct for the interaction of head motion and magnetic field inhomogeneities (susceptibility-by-movement interaction) the unwarping procedure of SPM8 was used. We assessed stimulation-induced head movement by comparing translational and rotational movement parameters separately for the hand and face pain condition. Separate 2 × 3 rmANOVAs (factor *stimulation* [hand/face] × factor *dimension* [x/y/z]) of the mean movement parameters during different conditions revealed no significant effect of stimulation neither for translation ($F(2, 56) = 2.45$, $p = 0.10$) nor rotation ($F(2, 56) = 1.95$, $p = 0.15$). Thus the two types of painful stimulations did not induce significantly different head movement. The maximum amount of head motion did not exceed 1 mm in any of the participants. The anatomical volume was coregistered to the mean echo-planar image and segmented with bias regularization set to medium level. Structural and functional volumes were normalized to standard Montreal Neurological Institute (MNI) space using the transformation matrix obtained from the segmentation procedure and resampled to a voxel size of 2 × 2 × 2 mm with an in-plane resolution of 2 mm. Functional images were finally smoothed with an 8 mm Gaussian kernel with FWHM.

*fMRI statistical analyses*

Neural data analysis was performed using the general linear model (GLM). On subject level, the applied model for the categorization task (encoding phase) contained two regressors of interest that coded for the two experimental conditions: (1) presentation of images with hand pain ('hand pictures') and (2) presentation of images with face pain ('face pictures'). Two regressors of no interest were added to the model that coded for the anticipation phase (white fixation cross presented before the picture) and rating period. All regressors were modeled with stick function and convolved with a canonical hemodynamic response function. Data were high-pass filtered with a cut-off period of 128 s. The effects of interest were tested using linear contrasts of the parameter estimates for the two regressors of interest, resulting in a t-statistic for each voxel. Further, contrast images for both conditions and differential contrasts (e.g. ['face pictures'] > ['hand pictures']) were generated for each participant and included into a second GLM. For group level analyses we used a random-effects approach using a one sample *t*-test (Friston et al., 1999) treating inter-subject variability as a random factor.

In order to assess neural activation related to successful memory formation (subsequent memory effect, SME) (Brewer et al., 1998; Kim,

2011) a second analysis was performed. Images within the categorization task were classified into remembered (hits) or forgotten images (misses) according to the results from the recognition task. Thus, this model contained 4 regressors of interest: (1) 'hand pictures' hits, (2) 'hand pictures' misses, (3) 'face pictures' hits, and (4) 'face pictures' misses. Two regressors of no interest coding for the anticipation phase and the rating period were added to the model. At first level the following contrast c = (−1, 1, 1, −1) ([SME 'face pictures' > SME 'hand pictures'] = ['face pictures' hits > 'face pictures' misses] > ['hand pictures' hits > 'hand pictures' misses]) was generated. In order to test for brain regions showing greater SMEs during face pain compared to hand pain the individual first level images were then compared against the hypothesis using a one-sample *t*-test at second level. In a second step, this second level model was extended by including the individual difference of fear between face and hand pain as a covariate of interest. Using this covariate we then tested for regions showing a correlation between SME 'face pictures' > SME 'hand pictures' and fear of face pain − fear of hand pain (c = 0, 1 at second level). The threshold for all statistical analyses was set to $p < 0.05$, familywise error (FWE, peak-level). Only for visualization purposes in all figures the threshold was set to $p = 0.001$ uncorrected. Please note that only brain activations surviving correction for multiple comparisons are reported and discussed in the "Results" and "Discussion" sections. Correction for multiple comparisons was based on regions of interest (ROIs), which were defined based on previous studies that had addressed the interaction of pain, visual processing, memory encoding and recognition (Bingel et al., 2007; Forkmann et al., 2013). Specifically, ROIs included the fusiform gyrus, LOC, parahippocampal gyrus and the hippocampus. ROIs with a 20 mm-diameter sphere were centered on peak-coordinates reported in these previous studies. The small volume correction of the amygdala was performed using an anatomical mask (http://neuro.imm.dtu.dk/wiki/Harvard-Oxford_Atlas).

*Psychophysiological interaction analysis.* Compared to hand pain, face pain led to higher fear ratings in our behavioral pilot study (hand: 21.74 ± 9.81; face: 34.35 ± 23.01 (M ± SD); $t(16) = -2.86$, $p = 0.01$) and the fMRI study (see "Results" section). Furthermore amygdala activation was increased for face compared to hand pain (contrast ['face pictures' > 'hand pictures']); see "Results" section; Table 3). Based on these observations, the amygdala's established role in (i) affective pain processing (Morris et al., 1998; Sergerie et al., 2008) and (ii) memory encoding of emotional stimuli (Dolcos et al., 2004; Phelps, 2004), we investigated changes in functional connectivity between the amygdala and task-relevant areas as a function of pain-related fear.

To this end, a psychophysiological interaction (PPI) analysis (Friston et al., 1997) was performed to explore differences in functional connectivity of the left and right amygdalae that might underlie the differential effects of face and hand painful stimulation on visual processing and visual encoding. Blood oxygenation level-dependent time series were extracted from a sphere located in the left (10 mm diameter, centered on the peak voxel (x y z) = (−26 −6 −23)) and right amygdala (10 mm diameter, centered on the peak voxel (x y z) = (22 −6 −23)) as identified in the contrast ['face pictures' > 'hand pictures'] for each subject individually using the first eigen time series (principal component analysis). The PPI regressor was calculated using the element-by-element product of the mean-corrected activation of the left and right amygdala (extracted time series) and the vector coding for the psychological variable (−1 on regressor 'hand pictures', 1 on regressor 'face pictures'). Individual PPI regressors were subsequently entered into one-sample *t*-tests to test for condition-specific differences in functional connectivity between both amygdala peak coordinates and any other brain region. We predicted an increased functional connectivity between the amygdala and task-relevant brain areas, such as LOC and fusiform gyrus for the facial compared to the hand pain stimulation. Corrections in these regions were based on anatomical masks and 20-mm-diameter spheres centered on peak coordinates reported in previous studies (Bingel et al., 2007; Forkmann et al., 2013).

## Results

### *Behavioral results*

#### *Behavioral pilot study results*

Paired *t*-tests revealed significantly higher electrical pain thresholds (hand: 1.89 ± 0.98 mA, face: 0.96 ± 0.42 mA; $t(13) = 4.02$, $p = 0.001$) and stimulation intensities corresponding to VAS 70 (hand: 2.14 ± 2.02 mA, face: 1.39 ± 0.1.28 mA; $t(16) = 2.78$, $p = 0.01$) for hand compared to face pain stimulation. Furthermore, there were significant differences between recalibrated stimulation levels that were used during the main task (hand: 3.83 ± 3.74 mA, face: 1.93 ± 1.71 mA; $t(16) = 3.03$, $p = 0.008$). However, pain intensity ratings were comparable between both conditions (hand: 59.26 ± 15.59, face: 56.74 ± 13.24; $t(16) = 1.60$, $p = .13$), confirming that the stimulation was perceived as equally intense at both stimulation sites.

Paired *t*-tests revealed no significant differences in categorization performance between conditions (hand: 94.71 ± 5.72%; face: 90.59 ± 8.64%; $t(16) = 1.53$, $p = 0.15$) but RTs were significantly slower (hand: 938.47 ± 190.44 ms; face: 1003.17 ± 221.09 ms; $t(16) = -2.94$, $p = 0.01$) and omission rates significantly higher (hand: 0.29 ± 1.21%; face: 3.53 ± 4.24%; $t(16) = -2.86$, $p = 0.01$) for face compared to hand pain stimulation in the categorization task (encoding phase; see Fig. 2). In the subsequently performed recognition test we found no significant differences between pictures that had previously been paired with painful face pain stimulation and those combined with hand pain stimuli neither for accuracy (hand: 54.41 ± 14.56%; face: 55.88 ± 9.56%; $t(16) = -0.37$, $p = 0.71$) nor for d′ (hand: 1.15 ± 0.47; face: 1.18 ± 0.40; $t(16) = -0.30$, $p = 0.77$).

#### *fMRI study results*

*Pain thresholds, stimulation intensities and pain intensity ratings.* Electrical pain thresholds (hand: 2.46 ± 1.22 mA, face: 0.98 ± 0.41 mA; $t(25) = 7.23$, $p < 0.001$) and stimulation intensities corresponding to VAS 70 (hand: 2.21 ± 1.38 mA, face: 1.09 ± 0.87 mA; $t(25) = 4.87$, $p < 0.001$) were significantly higher for hand compared to face pain stimulation. There were no significant differences between recalibrated stimulation levels that were used during the main task (hand: 4.32 ± 2.72 mA, face: 3.51 ± 2.85 mA; $t(25) = 1.90$, $p = 0.07$). Pain intensity ratings were comparable between both conditions (hand: 56.45 ± 13.75, face: 57.92 ± 10.63; $t(25) = -0.51$, $p = 0.61$). Note that applied stimulation intensities and VAS ratings did not differ between the pilot and fMRI study.

*Fear and expectation ratings.* Fear ratings assessed directly before the encoding task were significantly higher for the upcoming face pain stimulation than for hand pain stimulation (hand: 15.54 ± 15.70, face: 29.30 ± 19.71; $t(25) = -4.65$, $p < 0.001$). The subjects expected face pain to decrease their task performance significantly (−10.19 ± 14.31, $t(25) = -3.63$, $p = 0.001$) while hand pain was expected to have no influence (−1.12 ± 9.77, $t(25) = -0.58$, $p = 0.57$). These expectation ratings differed significantly ($t(25) = 3.71$, $p = 0.001$). Moreover, the participants expected a decrease in pain intensity for hand pain stimuli (−8.35 ± 11.34, $t(25) = -3.75$, $p = 0.001$) but no change for face pain stimuli (−2.73 ± 12.02, $t(25) = -1.16$, $p = 0.26$) while performing the task. Again, both pain perception expectation ratings differed significantly ($t(25) = -2.34$, $p = 0.02$).

*Categorization task (encoding phase): accuracy and RT.* There were no significant differences in categorization hits ('hand pictures' hits: 89.04 ± 10.45%, 'face pictures' hits: 92.24 ± 8.06%; $t(25) = -1.67$, $p = 0.10$) and omissions ('hand pictures' misses: 1.54 ± 2.75%, 'face pictures'

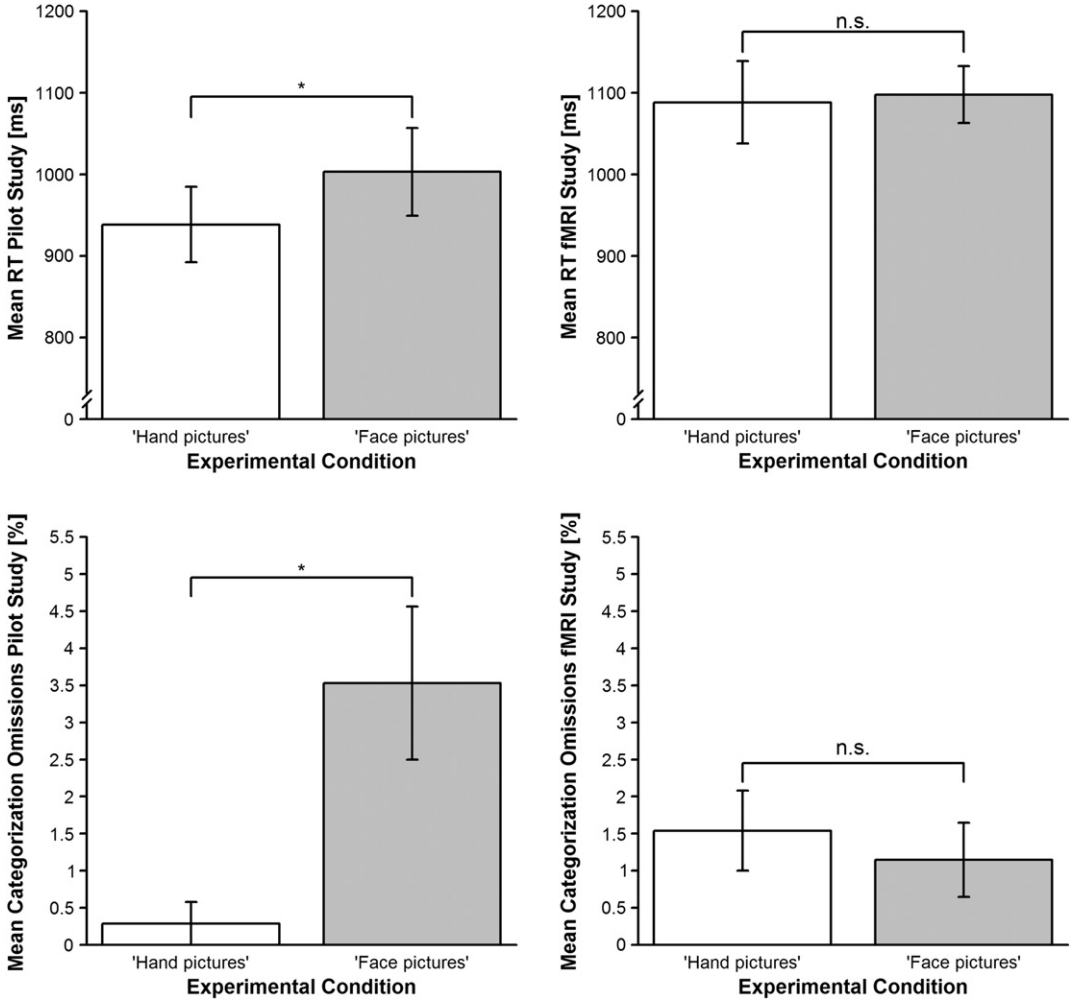


**Fig. 2.** Top: Mean reaction times in the pilot study (left) and the fMRI study (right). Mean RTs for images were significantly increased for pictures that were presented with face pain than for pictures that were presented with hand pain in the behavioral pilot study but not in the fMRI study. Bottom: Mean categorization omissions for the pilot study (left) and the fMRI study (right). Mean omissions for face pain pictures were significantly higher than for hand pain pictures in the behavioral pilot study but not in the fMRI study. Displayed are means ± SEM.

misses: 1.15 ± 2.57%; $t(25) = 0.63$, $p = .054$; see Fig. 2) between painful hand and face stimulation. Furthermore, there were no differences in the RTs between both experimental conditions (RTs 'hand pictures': 1088.30 ± 256.37 ms, RTs 'face pictures': 1097.67 ± 177.88 ms; $t(25) = -0.18$, $p = 0.86$; see Fig. 2).

*Recognition task.* Recognition performance did not differ between both experimental conditions (hits hand: 67.20 ± 17.06%, hits face: 66.21 ± 14.26%; $t(25) = 0.33$, $p = 0.75$; $d'$: hand: 1.21 ± 0.50, face: 1.37 ± 1.35; $t(25) = -0.57$, $p = 0.57$).

**Table 1**
Questionnaire data (mean and standard deviation (SD)).

| Questionnaire | Mean (SD) |
|---|---|
| ADS-K | 4.96 (5.63) |
| STAI state | 27.77 (4.76) |
| STAI trait | 30.27 (6.58) |
| PCS | 10.38 (6.74) |
| PASS 1, 2, 3, 4 | 12.73 (7.39), 16.63 (5.11), 6.35 (5.28), 7.65 (6.46) |
| PVAQ | 37.19 (8.70) |

ADS-K: Center for Epidemiological Studies Depression Scale; STAI: State Trait Anxiety Inventory; PCS: Pain Catastrophizing Scale; PASS: Pain Anxiety Symptom Scale; PVAQ: Pain Vigilance and Awareness Questionnaire.

*Psychological questionnaires.* Questionnaire data (M ± SD) are given in Table 1. None of the calculated correlations survived correction for multiple comparisons.

### Imaging results

#### Pain-related and encoding-related activity

Painful stimulation (pooled across face and hand pain stimulations) induced wide-spread activation in areas typically known for pain processing, such as bilateral insula, thalamus and cingulate cortex, and secondary somatosensory cortex (SII) (Apkarian et al., 2005; Tracey and Mantyh, 2007). Simultaneous visual stimulation activated brain regions well-known for visual processing, object identification and memory encoding such as bilateral hippocampal and parahippocampal gyrus and bilateral fusiform gyrus (Bingel et al., 2007; Forkmann et al., 2013). Peak coordinates of activated brain regions are given in Table 2.

#### Differences in effects of face and hand pain stimulation on visual processing and memory encoding

To test for differential neural activations in brain regions implicated in visual processing and memory encoding for face compared to hand pain stimulation, we compared both experimental conditions. Contrary to our hypothesis we did not observe reduced activation in the medial temporal lobe (MTL) or visual processing areas. Instead, the right anterior insula and the primary somatosensory cortex showed increased

**Table 2**
Stimulus-related and task-related neural activity in the categorization task.

| | Coordinates (in mm) | | Voxel level (T) (left/right) |
|---|---|---|---|
| | Left | Right | |
| Region | x y z | x y z | |
| LOC | −40 −74 −9 | 40 −78 7 | 13.92/16.66 |
| Occipital gyrus | −42 −80 1 | 40 −78 7 | 13.89/16.66 |
| Fusiform gyrus | −30 −58 −13 | 34 −58 −11 | 17.29/15.86 |
| SII | −64 −18 17 | 50 −16 17 | 10.66/12.96 |
| Cerebellum | −4 −74 −21 | 8 −72 −19 | 12.41/11.14 |
| Thalamus | −8 −18 11 | 12 −18 9 | 10.05/11.71 |
| SMA | −12 4 61 | 2 8 59 | 7.0/11.45 |
| Posterior Insula | −40 −14 15 | 38 −14 17 | 8.28/11.09 |
| Anterior Insula | −34 16 3 | 34 16 9 | 5.77*/7.25 |
| Brainstem | −4 −32 −25 | 6 −30 −21 | 10.46/7.8 |
| Precuneus | −24 −68 41 | 20 −60 45 | 10.43/9.5 |
| Parahippocampus posterior | −36 −34 −19 | 34 −32 −23 | 7.16/9.59 |
| MCC | – | 10 20 35 | –/7.3 |
| Hippocampus | −22 −32 −11 | 22 −34 −5 | 5.41*/6.74 |
| Amygdala | −28 0 −19 | 26 2 −19 | 4.26*/3.75* |

SII, secondary somatosensory cortex; SMA, supplementary motor area; LOC, lateral occipital complex; MCC, midcingulate cortex.
* T-values corrected using small volume correction (SVC) in a-priori regions of interest (see "Methods" section) at an FWE corrected level of $p < 0.05$ while no asterisk indicates FWE correction with $p < 0.05$ at whole-brain level.

activation during hand compared to face pain stimulation ['face pictures' < 'hand pictures']. The reverse contrast ['face pictures' > 'hand pictures'] revealed that face pain stimulation compared to hand pain stimulation was associated with higher neural activity in bilateral fusiform gyrus, right precuneus and LOC, areas known for visual processing and object identification. Further we found higher activity in the bilateral hippocampal and parahippocampal gyrus, which are implicated in memory encoding and in the bilateral amygdala, which is well known for the processing of fear and emotional stimuli, and the left thalamus. Peak coordinates and t-values are given in Table 3. To further investigate the influence of fear and the higher amygdala activation for face pain we extracted parameter estimates from amygdala peak coordinates ['face pictures' > 'hand pictures'] with 5 mm radius spheres using the Marsbar toolbox in Matlab (mathworks.com) and performed correlation analyses. Across subjects, activation in the right amygdala showed a significant correlation with subjective differences in fear ratings between face and hand pain conditions ([22 −6 −23], $r = 0.44$, $p = 0.03$, see Fig. 3) indicating increased amygdala activation for the subjects, who perceived face stimulation as more threatening than hand stimulation. Correlation analyses with the left amygdala peak coordinate revealed no significant results ([−26 −6 −23], $r = 0.30$, $p = 0.16$).

In the next step we tested for differences in the subsequent memory effect (SME) during face compared to hand pain stimulation (['face pictures' hits > 'face pictures' misses] > ['hand pictures' hits > 'hand pictures' misses]). This analysis revealed no significant differences in neural activation. However, as we observed higher subjective fear ratings for face pain as well as higher activation of the MTL during painful stimulation (irrespective of the behavioral performance), we included differences in fear as a covariate (fear rating face pain > fear rating hand pain) and tested its influence on the SME contrast. In this correlation analysis, the left hippocampal gyrus [(−28, −16, −13), $t = 6.6$, $p < 0.05$, SVC] showed significant activation (see Fig. 4), indicating that stronger differences in fear ratings between the face and hand pain stimulation correlated with stronger difference in hippocampal activation between both conditions during memory encoding. In other words, the more participants feared face over hand pain stimulation, the higher the memory-related hippocampal activity during face compared to hand stimulation.

**Table 3**
Stimulus-specific neural activations.

| | Coordinates (in mm) | | Voxel level (T) (left/right) |
|---|---|---|---|
| | Left | Right | |
| Region | x y z | x y z | |
| 'Face pictures' > 'hand pictures' | | | |
| Brainstem | −10 −20 −21 | – | 5.58*/– |
| Thalamus | −14 −34 −1 | – | 5.39*/– |
| Precuneus | – | 8 −54 7 | –/4.8* |
| Parahippocampus | −24 −38 −15 | 24 −36 −15 | 4.79*/3.87* |
| LOC | −48 −60 −5 | 50 −66 −1 | 3.83**/4.36** |
| Hippocampus | −28 −8 −23 | 24 −6 −27 | 4.06*/4.46* |
| Fusiform | −28 −32 −27 | 26 −54 −13 | 4.36*/4.28* |
| Amygdala | −26 −6 −23 | 22 −6 −23 | 4.32*/4.01* |
| 'Hand pictures' > 'face pictures' | | | |
| SI | – | 38 −28 61 | –/7.51 |
| Insula | – | 40 −20 19 | –/6.88 |

LOC, lateral occipital complex; SI, primary somatosensory cortex.
* T-values corrected using small volume correction (SVC) in a-priori regions of interest (see "Methods" section) at an FWE corrected level of $p < 0.05$ while no asterisk indicates FWE correction with $p < 0.05$ at whole-brain level.
** SVC using spheres.

*PPI analysis*

The PPI analysis investigating condition-specific changes in functional connectivity between the left amygdala [(−26, −6, −23), see Fig. 5] and any other brain region revealed a significant connectivity increase between the left amygdala and areas relevant for visual processing and memory encoding during face compared to hand pain stimulation (contrast [face pictures > hand pictures]). In particular functional connectivity was enhanced for the left lingual gyrus [(−28, −80, −13), $t = 3.89$, $p < 0.05$, SVC], right fusiform gyrus [(28, −66, −11), $t = 4.01$, $p < 0.05$, SVC] and left posterior parahippocampal gyrus [(−22, −54, −9), $t = 7.15$, $p < 0.05$, SVC]. Moreover, we found an increase in functional connectivity with visual ventral regions corresponding to the LOC [(−44, −70, −11), $t = 5.41$, $p < 0.05$ corrected, SVC], a functional area implicated in object recognition (see Fig. 5). In contrast, no changes in functional connectivity were observed between the left amygdala and other brain regions for the reverse contrast [hand pictures > face pictures]. Further, no differences in functional connectivity were found with the right amygdala as a seed region. Finally, to further explore the functional relevance of the observed connectivity differences we performed correlational anaylses of recognition performance and parameter estimates of the LOC. The individual connectivity strength between the left amygdala and the left LOC was positively correlated with the individual difference in recognition performance between conditions (recognition hits 'face pictures' > recognition hits 'hand pictures'; $r = 0.45$, $p = 0.03$) (see Fig. 5). This indicates that larger differences in recognition performance between conditions were associated with larger condition differences in functional connectivity between amygdala and visual areas.

## Discussion

Here we investigated the effects of face compared to hand pain on visual processing, memory encoding and recognition in young healthy volunteers. As expected, we found higher fear ratings for face compared to hand pain stimulation. On the neural level this result was supported by higher amygdala activation for the face compared to hand pain condition that scaled with the difference in perceived pain-related fear. However, contrary to our hypothesis, face pain did not lead to compromised categorization and recognition performance and did not decrease neural activity in visual and memory encoding-related areas compared to hand pain. Instead, face pain led to increased brain activation in areas involved in visual processing (i.e. LOC) and memory encoding in the MTL (i.e. hippocampus and parahippocampus). Furthermore, hippocampal activity related to greater recognition performance during face compared to hand stimulation was associated with condition-specific

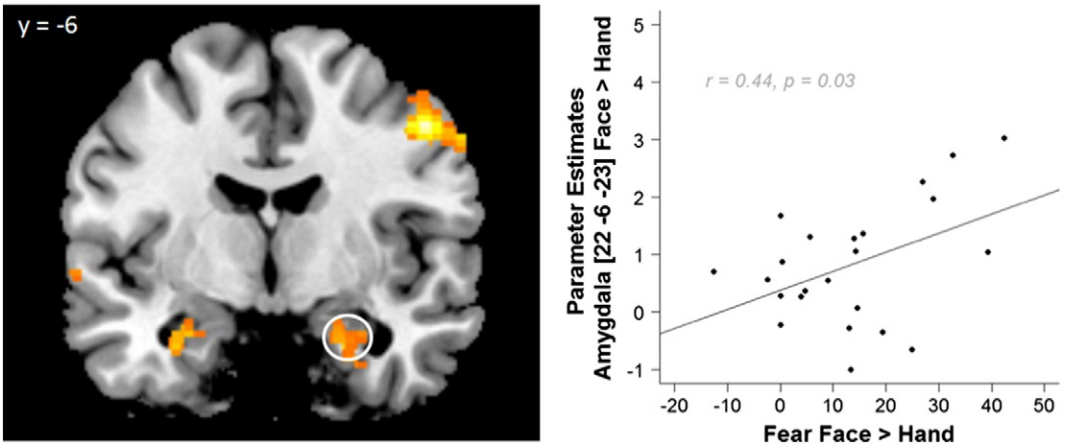


**Fig. 3.** Left: Right amygdala [22 −6 −23] was significantly more activated during face compared to hand pain stimulation. T-maps are overlaid on an MNI template. For visualization purposes, images are thresholded at $p < 0.001$ uncorrected. Right: Differences in amygdala activation (face > hand) [22 −6 −23] correlated with differences in fear ratings between both experimental conditions (face − hand). Higher fear ratings for face compared to hand pain were associated with stronger right amygdala activation in the respective conditions.

differences in pain-related fear. Finally, we found enhanced functional connectivity between the left amygdala and task-relevant areas, such as the LOC, for face compared to hand pain, which was related to less pain-induced recognition impairment during face stimulation. The larger cortical activation in the primary somatosensory cortex (and insula) for hand pain compared to facial pain is in line with the known larger cortical representation of the hand area (Penfield and Boldrey, 1937), compared to the forehead.

*Compensatory neural activation for face pain pictures and behavioral performance*

Our behavioral pilot study results had suggested that the face stimulation disturbs visual categorization more than hand pain. We therefore expected similar behavioral results in our fMRI study. However, we found no behavioral differences between both experimental conditions, neither in the categorization nor in the surprise recognition task. Possible explanations for this absence of behavioral differences might be higher arousal levels in the scanner environment or the overall very high correct categorization rates, which implies that the task might have been easy to perform, even in the presence of pain. However, the fact that the same experimental paradigm has been used in a previous study that showed a robust interruptive effect of pain on visual categorization, memory encoding and recognition renders the latter explanation unlikely (Forkmann et al., 2013). Although the stimulation site had no effect on task performance, we found an interesting difference in the way the participants perceived the two conditions on the emotional level. Across the participants, the face stimulation was perceived as more fear-inducing than the hand stimulation. This finding is remarkable, particularly in combination with our second unexpected finding of increased instead of decreased neural activity in task-related and memory encoding-related brain areas, such as the LOC and subregions of the MTL (i.e. hippocampus), for pictures presented with face pain compared to those presented with hand pain. According to the *attentional control theory of anxiety* (Eysenck et al., 2007), compensatory strategies such as enhanced resource usage or increased effort are activated to counter anxiety-induced performance impairment. Although speculative at this stage, we suggest with reference to this theoretical framework that the increase in neural activity in the face pain condition might reflect fear-induced compensatory activation of task-related brain regions to maintain cognitive performance. The attentional control theory of anxiety has been supported by various studies (Derakshan et al., 2009; Johnson and Gronlund, 2009; Edwards et al., 2015). For instance, Ansari and Derakshan (2011) showed increased cognitive effort and neural activation in high-anxious subjects in an anti- and prosaccade task. Compensatory neural activation and

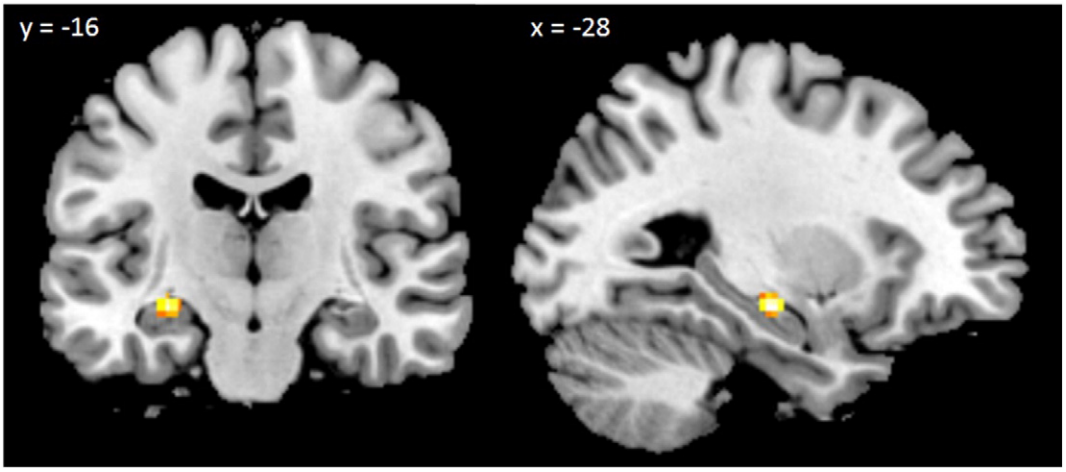


**Fig. 4.** Higher fear ratings for facial compared to hand pain were associated with stronger differential subsequent memory effects (contrast ['face pictures' subsequent hits > subsequent misses > 'hand pictures' subsequent hits > subsequent misses]) in the left hippocampus. T-maps are overlaid on an MNI template. For visualization purposes, images are thresholded at $p < 0.001$ uncorrected.

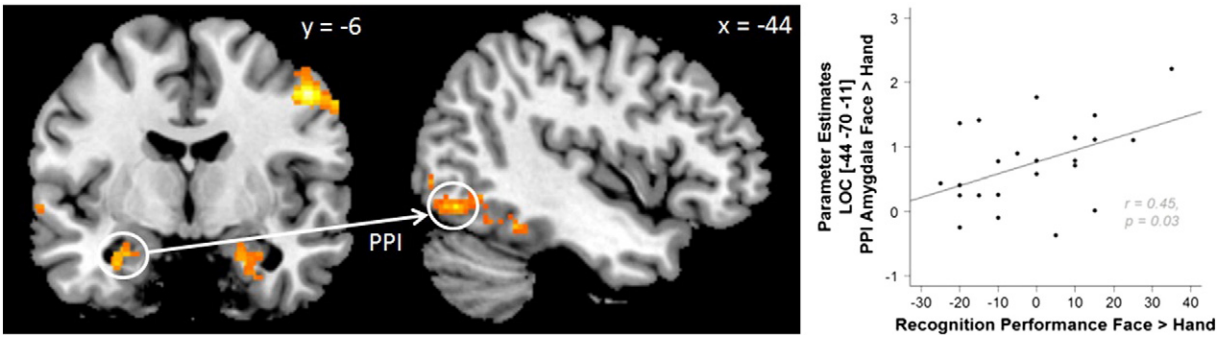


**Fig. 5.** Left: Psychophysiological interaction analysis. Functional connectivity between the left amygdala and the left LOC is higher for facial compared to hand pain stimulation. The left amygdala ("source") was defined as a sphere (10 mm diameter) centered around the peak voxel [(*x*, *y*, *z*)(−26 −6 23)]. This region showed a body site-specific modulation as indicated by the contrast [('face pictures') > ('hand pictures'); see "Results" section]. T-maps are overlaid on an MNI template. For visualization purposes, thresholded at $p < 0.001$ uncorrected. Right: Functional connectivity between amygdala and LOC for face compared to hand pain during encoding was related to better visual encoding as indicated in higher recognition performance for face than for hand stimulation.

strategies are also known from neurological disorders and aging. Gour et al. (2011) reported compensatory brain activity in the anterior temporal network of patients with mild cognitive impairment and Alzheimer's disease compared to healthy participants. Anterior temporal network activation (including hippocampus and amygdala) was enhanced and resting state connectivity within this network correlated positively with memory performance. Patients with idiopathic Parkinson's disease have shown higher neural activation compared to healthy elderly subjects in a working memory task (Caminiti et al., 2015) and high-performing compared to low-performing older adults demonstrate a reorganization of neurocognitive networks (Cabeza et al., 2002).

### *Fear, memory encoding and the amygdala*

As mentioned in the previous paragraph, pain-related fear ratings were significantly higher for face pain compared to hand pain. This is in line with findings from our behavioral pilot study and a recent study investigating increased sensitization for face compared to hand pain (Schmidt et al., 2015). This higher threat value of face pain might be explained by the exceptional biological relevance of pain located in the head and facial area which house vital functions such as breathing and food intake. In support of this notion, Sambo et al. (2012) reported an increased defensive response (i.e. the hand-blink-reflex) when a painfully stimulated hand was positioned near the face as compared to a position further away from the face. It is conceivable that unspecific factors such as unpleasantness or arousal associated with the nociceptive information, which were not assessed in our study, might have contributed to our results. Future studies should explore the influence of these factors to the differential effects of facial compared to hand pain on visual processing.

The right amygdala showed fear-related activation that was increased for face compared to hand pain. This brain area plays an important role in emotional processing and memory encoding improvement of emotional and fear-related events and threat-related stimuli (LeDoux, 2003; Dolcos et al., 2004; Phelps, 2004). In line with our findings of increased activity in the amygdala and visual areas possibly due to higher fear for face pain pictures, Ousdal et al. (2014) reported increased activation and functional connectivity between amygdala and visual areas in participants with higher state anxiety. Analyses of the subsequent memory effect (i.e. brain activation during encoding [recognition hits > recognition misses]) revealed that hippocampal activity related to greater recognition performance during face compared to hand stimulation was positively correlated with condition-specific differences in pain-related fear. This result again underlines the influence of threat on cognitive performance and provides further evidence for fear-driven compensatory neural activation to achieve stable behavioral performance, since we observed no differences in recognition performance between both conditions.

In addition, we found enhanced functional connectivity between the left amygdala and the LOC, lingual, parahippocampal and fusiform gyrus for pictures that were presented with face pain compared to hand pain, all areas known to be involved in visual processing, memory encoding and object recognition (Machielsen et al., 2000; Bingel et al., 2007; Forkmann et al., 2013). The LOC was defined based on coordinates reported by Bingel et al. (2007), who determined this area specifically for object recognition as they found a main effect of object visibility in their task. With reference to this previous finding and our observation in the present study we suggest that the increased functional connectivity between amygdala and LOC contributes to successful memory encoding of face compared to hand pain pictures. In line with this assumption, we found a significant positive correlation between activation in the LOC and behavioral performance in the recognition task. More specifically, we observed higher recognition rates with higher functional connectivity between amygdala and LOC for face compared to hand pain pictures. Although we found no difference in recognition accuracy at the behavioral level between both conditions, recent studies using the same recognition task showed stable effects of experimentally induced pain on recognition accuracy (Bingel et al., 2007; Forkmann et al., 2013). In support of the idea of fear-driven enhanced functional connectivity in our study, there are studies showing that functional connectivity between task-related areas is enhanced for fearful events. Furl et al. (2013) investigated effective connectivity between the amygdala and task-relevant areas during the processing of fearful faces. They report that fear modulated connections from the amygdala to task-relevant areas (e.g. the fusiform face area) and conclude that the amygdala seems to control the coding of behaviorally relevant information in task-relevant areas. A similar influence of the amygdala has been reported in other studies (Morris et al., 1998; Vuilleumier et al., 2004; Hadj-Bouziane et al., 2012).

These interpretations should be seen in light of the fact that the PPI analysis was exploratory in nature and that our two key amygdala findings were not consistent as the correlation between condition-specific differences in BOLD activity and pain-related fear was observed in the right amygdala whereas the condition-related differences in connectivity with task-related areas were found in the left amygdala. However, we feel that these different pieces of evidence lend support to the notion that pain-related fear and the engagement of fear-related brain areas such as the amygdala might be important in the context of facial pain processing.

## Conclusion

In this study we show increased neural activity during visual object categorization in the presence of face compared to hand pain in brain

areas involved in visual processing (LOC) and encoding (e.g. *hippocampus*) but no difference in behavioral performance. Further, the increased fear for face pain influenced memory encoding at the neural level and functional connectivity with visual processing areas. These findings might be interpreted as fear-driven compensatory resource activation. The role of increased fear (sensitivity) for pain-induced memory disturbances in patients suffering from recurrent or chronic headache or facial pain warrants further investigation.

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