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Expectation influences the interruptive function of pain: Behavioural and neural findings

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Abstract

Background: Expectations can dramatically influence the perception of pain, as has been shown in placebo analgesia or nocebo hyperalgesia. Here, we investigated the role of expectation on the interruptive function of pain – the negative consequences of pain on cognitive task performance – in 42 healthy human subjects.
Methods: Verbal and written instructions were used to manipulate the subjects' expectation of how pain would influence their task performance in an established visual categorization task which was performed with or without concomitant painful thermal stimulation during 3T fMRI scanning. The categorization task was followed by a surprise recognition task.
Results: We observed a significant interaction between stimulation (pain/no pain) and expectancy (positive expectation/negative expectation): categorization accuracy decreased during painful stimulation in the negative expectancy group ($N = 21$), while no difference was observed in the positive expectancy group ($N = 21$). On the neural level, the positive expectancy group showed stronger activity in the anterior cingulate cortex (ACC) and hippocampus during painful stimulation compared to the negative group. Moreover, we detected a decrease in connectivity between ACC and fusiform gyrus during painful stimulation in the negative expectancy group, which was absent in the positive expectancy group.
Conclusion: Taken together, our data show that expectation can modulate the effect of pain on task performance and that these expectancy effects on the interruptive function of pain are mediated by activity and connectivity changes in brain areas involved in pain processing and task performance. The possibility of changing cognitive task performance by verbal information in clinical population warrants further investigation.
Significance: We show that the interruptive function of pain on concurrent visual task performance is influenced by expectation. Positive expectation can abolish the detrimental effects of pain on cognition. These expectancy effects on the interruptive function of pain are mediated by changes in functional connectivity between rostral ACC, posterior fusiform cortex and the hippocampus.

1. Introduction

Painful stimuli automatically attract attention and interfere with ongoing cognitive processes, which, in most cases, results in impaired cognitive performance. This process termed the 'interruptive function of pain' (Eccleston and Crombez, 1999) has

been demonstrated for acute, experimental (Moore et al., 2012) and clinical (Kuhajda et al., 2002) pain as well as for chronic pain (Eccleston, 1995; Grisart et al., 2007). Besides the physical properties of the stimulus like stimulus intensity (Buhle and Wager, 2010) or stimulus novelty (Legrain et al., 2009), cognitive processes determine the interruptive function of pain, including stimulus predictability (Crombez et al., 1994), pain catastrophizing (Grisart and Plaghki, 1999; Van Damme et al., 2004; Vancleef and Peters, 2006) and pain-related threat (Crombez et al., 1998). Here, we investigate whether expectations modulate the effect of pain on behavioural and neural markers of cognitive performance. The influence of expectations on pain perception has widely been studied in a number of experimental paradigms. A prime example is placebo analgesia, the experience of pain relief induced by the administration of an inert substance combined with the expectation of pain reduction (Benedetti et al., 2005; Enck et al., 2008). Conversely, negative expectations can lead to an enhanced perception of pain as evident in nocebo hyperalgesia (Atlas and Wager, 2012).

In contrast, the influence of expectations on the interruptive function of pain has not received much attention yet. Boselie et al. (2014) reported that the interruptive function of pain is modulated by optimism, which is defined as an implicit or unspecific expectation of something positive to happen (Scheier and Carver, 1985). In a previous study, we observed differences in the interruptive effect of experimental pain, which were – at least in part – explained by differences in subjects' individual expectations of how pain would affect their performance without any explicit manipulation of expectancy (Sinke et al., 2015). These findings support the notion that expectation can influence the mostly negative effects of pain on cognitive task performance.

Here, we explored the neural mechanisms underlying the modulatory influence of expectation on pain-induced changes in cognitive task performance using a visual categorization and surprise recognition task and functional magnet resonance imaging (fMRI) in healthy subjects. Using a between-subject design, we induced either positive or negative expectations by providing standardized verbal and written information that pain would either improve or impair task performance. We did not include a neutral condition, as the default assumption of how pain affects cognitive performance seems to be negative (Forkmann et al., 2016; Sinke et al., 2015). Neutral and negative expectation groups might therefore be quite similar in terms of expectation. Without providing any information on the effect of pain (comparable to a neutral condition), pain has been shown to impair task performance in similar tasks (Forkmann et al., 2013, 2016), and genuine expectations correlated with these pain-induced task impairments. The visual categorization task in combination with simultaneous painful stimulation is well-suited to explore the behavioural and neural effects of individual expectations, since neural mechanisms of visual processing, pain perception and their interaction have been well characterized in previous studies (Bingel et al., 2007; Forkmann et al., 2013). We hypothesized that differences in expectation regarding the interruptive effect of pain modulate individual task performance and that these differences are mediated by changes in activation and connectivity within and between brain areas involved in pain processing, allocation of attention and visual task processing.

2. Materials and methods

2.1 Subjects

Behavioural and fMRI data were acquired in 48 healthy, right-handed subjects. Six subjects had to be excluded from data analyses for the following reasons: technical problems with the presentation computer ($n = 2$), non-compliance during pain rating ($n = 1$) and awareness of the expectancy manipulation ($n = 3$). These three participants were excluded from further analyses as they spontaneously informed us about being aware of the expectation manipulation. Data of the remaining 42 subjects (21 males; mean age: 25.4 ± 4.1 years ($M \pm SD$); range: 19–39 years, no difference between groups) were included in the final analyses. All subjects had normal heat pain thresholds at the site of stimulation (Rolke et al., 2006), reported normal hearing, and normal or corrected-to-normal vision and had not taken any analgesic medication on the day of the experiment. Subjects had no known history of neurological or psychiatric diseases, including recurrent or chronic pain. The study was conducted in accordance with the Declaration of Helsinki and had been approved by the local ethics committee (Medical Association Hamburg). All subjects gave written informed consent to participate, were free to withdraw from the study at any time and received a small monetary recompense for their participation.

2.2 Experimental paradigm

This study is part of a series of experiments investigating the influence of expectation on cognitive task performance (see also Sinke et al. (2016)). In these experiments, pain was used as a tool to manipulate expectation. The experimental paradigm is based on a paradigm we had used recently to explore pain-specific behavioural and neural effects on visual encoding and recognition (Forkmann et al., 2013). Here, this task was combined with the experimental manipulation of expectancy regarding the effects of pain on cognitive processes.

The study was performed on 2 days, with 1–6 days between the introductory and the experimental session. The delay between day 1 and day 2 did not differ between groups (positive manipulated group: 2.7 ± 1.9 days, negative manipulated group 3.8 ± 2.2 days, $t_{(40)} = 1.7$, n.s.). On the first day (introductory session), subjects were randomized into two groups. We induced either positive or negative expectations on how pain affects cognitive processes by providing different standardized verbal and written instructions (see Experimental Procedures). We chose to use a positive and a negative manipulation instead of a positive and a neutral condition for two reasons. First, we wanted to assure that both groups received a *directed* manipulation of their expectation during the experiment (and particularly during the preparatory procedure). Second, using a positive and negative manipulation allowed us to explore the extremes of expectancy manipulation in this proof-of-principle study. All subjects completed a number of preparatory procedures, including the assessment of heat pain thresholds, calibration of painful thermal stimuli and the assessment of anxiety, depression and pain-related personality traits (see Experimental Procedures) before they completed a short training session to practice the main task (categorization task). The actual fMRI experiment was conducted on day 2 and was divided into two parts: (1) the simultaneous presentation of visual and painful stimuli (encoding phase) inside the MRI scanner and (2) a subsequent surprise recognition task to test the effects of expectation and pain on memory retrieval outside the MRI scanner. Note that no painful stimuli were applied during the surprise recognition task.

2.3 Experimental procedures

2.3.1 Day 1

Subjects were welcomed and informed that the aim of the study was to study neural mechanisms involved in the interaction of pain perception and visual processing. Subsequently, standardized instructions were read out aloud by the experimenter to induce one of two different expectations. The positive expectancy group ($N = 21$) was informed that pain improves cognitive processes such as visual processing and working memory. The negative expectancy group ($N = 21$) was provided with the opposite information and was told that pain disturbs these cognitive processes. The instruction for the negative manipulation group emphasized that pain has been shown to attract attention and to decrease visual processing and memory processes in order to prevent future harm. As an everyday example, a situation was described, in which a person accidentally steps onto a nail. Perceiving pain would then automatically lead to an involuntary shift of attention towards the injured site in order to eliminate the threat and other, less relevant processes will be disrupted. The instruction for the positive manipulation group emphasized that pain has been shown to boost visual processing and memory processes in order to prevent future harm. Here, an everyday example described a situation, in which a person accidentally bumps into something. We emphasized that, in consequence, this person would walk more careful to prevent further injuries. Thus, pain was described to increase visual processing and memory, leading to better (task) performance. Both manipulations were supported by figures and references of fictive studies that showed the intended effect for visual processing and memory performance. Subjects then filled in a number of questionnaires (see below, Psychological questionnaires) assessing general anxiety and depression (ADS-K, State Trait Anxiety Inventory (STAI), trait scale), as well as questionnaires assessing pain-related psychological processing (Pain Vigilance and Awareness Questionnaire (PVAQ), Pain Anxiety Symptoms Scale (PASS-D), Pain Catastrophizing Scale (PCS)). Subjects were familiarized with the heat pain stimuli and the rating procedure used to indicate perceived pain intensity via a visual analogue scale (VAS, anchors: 0 = 'not painful at all'; 100 = 'unbearably painful'). Next, the individual heat pain threshold at the site of stimulus application (left inner forearm, 12 cm proximally from the wrist) was determined using the method of limits (Fruhstorfer et al., 1976) with ramped stimuli (1 °C/s increase in temperature, starting at a baseline of 35 °C and with an upper limit of 50 °C to avoid tissue damage). Subjects indicated the first painful sensation by pressing a button. The individual pain threshold was calculated using the mean

temperature of four repetitions. Then, a temperature calibration was conducted to determine the individual temperature level corresponding to an intensity level of 70 on the VAS (anchors: 0 = 'not painful at all'; 100 = 'unbearably painful'), which corresponds to moderate to severe pain levels that have previously been shown to impair visual object processing (Forkmann et al., 2013). To this end, subjects received heat stimuli of varying temperature levels around their individual pain threshold (duration 2.5 s; range: heat pain threshold − 1 °C < heat pain threshold < heat pain threshold + 3.5 °C, temperature difference of 0.5 °C, each temperature was applied twice). Following each stimulus, subjects rated the perceived intensity using a VAS on a computer screen by moving a red bar between the two endpoints of the VAS. A linear regression on subjective pain ratings was used to calculate the temperature that corresponded to an intensity level of 70.

2.3.2 Day 2

The fMRI experiment was conducted on the second day of the study. Subjects read the instructions once again, immediately before the MRI session. To ensure that the individually calibrated temperature still yielded a pain intensity of VAS 70 when applied inside the MR scanner, we presented three stimuli of the previously calibrated temperature. Subjects indicated the perceived intensity for each stimulus using a VAS. Temperatures were manually adjusted if the mean of the three intensity ratings differed significantly from 70. After this calibration check, subjects indicated their current mental state on a VAS assessing tiredness (0 = 'not tired at all'; 100 = 'extremely tired'), excitement (0 = 'relaxed'; 100 = 'extremely excited'), fear of pain (0 = 'not fearful at all'; 100 = 'extremely fearful') and their expectation of how pain would influence their performance (−5 = 'pain extremely impairs performance', 5 = 'pain extremely improves performance'; 0 = 'no influence'). For all VAS ratings, anchors were given in written form without numbers and the red indicator bar appeared at a random position on the VAS at the beginning of the rating. Subjects then performed the actual encoding task, which was introduced as a simple visual categorization task (duration ~ 10 min). Here, subjects were asked to categorize objects presented on pictures reduced in visibility (33%). Subjects had to indicate whether the image showed a living or a non-living object by pressing one of two buttons as quickly as possible without compromising on accuracy (categorization task). Pictures were presented alone ('control') or with concurrent painful thermal stimulation ('pain'). Each condition comprised 20 trials divided into four blocks of five consecutive stimuli of the same condition. Painful and pain-free (control) blocks showing living and non-living objects were presented in a pseudo-randomized order. Both pain and control stimuli were combined with the same number of living and non-living objects (i.e. 10 living and 10 non-living objects). Each trial started with the presentation of a white fixation cross (variable duration of 6.5 ± 1.5 s), followed by an image presented for 2.5 s and another fixation cross (variable duration of 4.5 ± 1.5 s; Fig. 1A). Subjects rated the intensity of the thermal stimulus applied in pain trials using a VAS that was presented after a variable break (3–6 s, white fixation cross). Categorization accuracy, response time (RT) and pain intensity ratings were recorded as behavioural outcome measures. The categorization task was followed by a surprise recognition task (duration ~14 min) that was performed outside the scanner. Subjects were asked to indicate their memory confidence for all previously presented pictures and the same number of new pictures using a 6-point confidence scale that was presented on a computer screen (surely old, probably old, unsure old, unsure new, probably new, surely new). Overall, 80 images (40 old and 40 new images) with full visibility were presented for 1.5 s each. After the picture presentation, the confidence scale was presented until subjects made their decision that triggered the next trial. Recognition accuracy was recorded as the behavioural outcome measure.

2.4 Stimuli

The presentation of the visual stimuli, application of the thermal stimuli and recording of the behavioural data was managed using the software Presentation (Presentation 16.3, Neurobehavioral Systems Inc, Berkley, CA, USA; www.neurobs.com).

2.4.1 Visual stimuli

The visual stimuli consisted of pictures showing natural scenes with living or non-living objects. We selected 40 pictures of living objects (animals) and 40 pictures of non-living objects (e.g. cars, buildings, dishes). One half of the pictures were presented during the encoding task while the other 50% served as new images (lures) in the recognition task. To increase the difficulty of the categorization task, image visibility was reduced to 33% using a

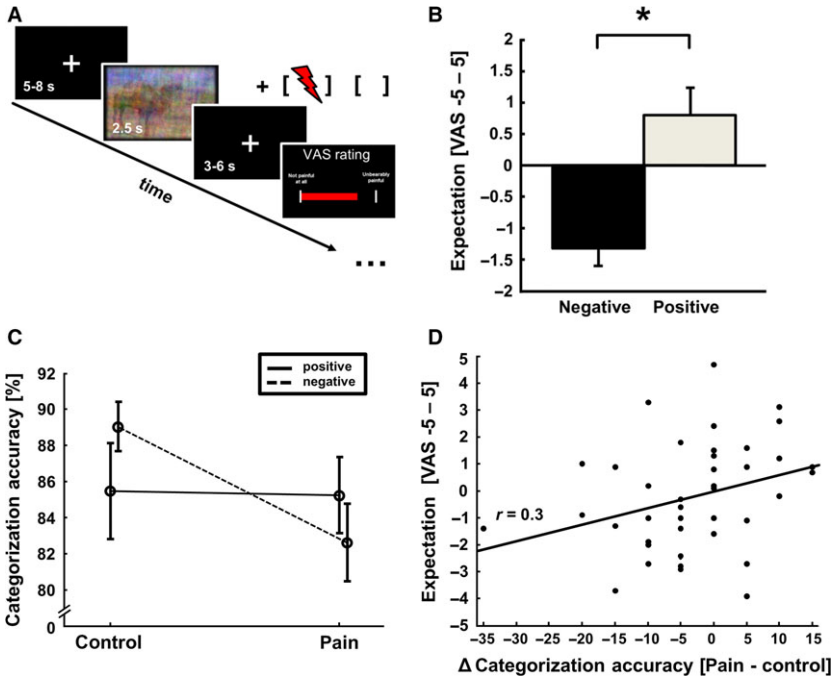

Figure 1 (A) Experimental paradigm. During the categorization task (encoding phase), 40 images of living or non-living objects were presented with reduced visibility (33%) for 2.5 s each. In half of the trials, heat pain stimuli (duration of 2.5 s) were applied simultaneously with the images. In the other 50% of the trials, images were presented without additional stimulation. Subjects rated the intensity of the painful stimulation after each trial using a visual analogue scale. (B) Expectancy manipulation. Subjects' expectancy was verbally manipulated and differed significantly between groups**.** Subjects in the negatively manipulated group expected pain to decrease their task performance. (C) Categorization performance varied depending on subjective expectancy. STIMULATION × EXPECTANCY interaction. Subjects' performance decreased during painful stimulation in the negative expectancy group, while no difference in categorization accuracy was detected in the positive expectancy group. (D) For visualization purposes, we plotted categorization accuracy against participants' expectation. The more subjects expected pain to impair their task performance the poorer they performed during concomitant painful stimulation.

scrambling routine as described previously (Rainer et al., 2001; Rose et al., 2005) while pictures were presented with full visibility in the recognition task. During the encoding phase, 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° and were displayed for 2.5 s. For the recognition task, pictures were presented on a Dell laptop computer with a visual angle of 12.4° × 9.4°.

2.4.2 Heat pain stimuli

We used an MR-compatible thermal device (PATHWAY model CHEPS; Medoc, Ramat Yishai, Israel) to apply brief, individually calibrated painful contact heat stimuli with a duration of 2.5 s (mean temperature: 48.1 °C ± 1.2 (M ± SD) ranging between 45.2 °C and 49.5 °C, perceived pain intensity (VAS): 71.9 ± 10.8 (M ± SD); no significant temperature difference between groups). The heating and cooling rates were set to 70 °C/s and 40 °C/s respectively. The CHEPS thermode (27 mm diameter) was attached to the middle of the left inner forearm using a bandage. The baseline temperature was set to 35 °C. To ensure the simultaneous perception of visual and heat stimuli and to account for the conduction velocities of pain fibres and a delay between triggering pain stimulation and actual stimulation, the delivery of the heat stimuli was triggered 470 ms before image presentation (see Forkmann et al., 2013).

2.5 Psychological questionnaires

To investigate the association of pain-related interference with distinct pain-related and other cognitive processes that are known to moderate the interruptive function of pain, subjects completed the German version of the following questionnaires assessing pain-related psychological processing: (1) PVAQ ((McCracken, 1997); German version:(Lautenbacher et al., 2009)); (2) PASS-D ((McCracken et al., 1992);

German version:(Walter et al., 2002); (3) PCS ((Sullivan et al., 1995); German version:(Lautenbacher et al., 2009); as well as the (4) Center for Epidemiological Studies–Depression Scale ((Radloff, 1977); German version: ADS-K, (Hautzinger and Bailer, 1993)); and (5) STAI ((Spielberger et al., 1983); German version:(Laux et al., 1992)). All questionnaires were analysed according to the respective manuals.

2.6 Analysis of behavioural data

Behavioural data were automatically recorded and logged by the stimulation program Presentation. All behavioural data analyses were conducted using SPSS (version 18.0, SPSS Inc., Chicago, Illinois, USA). Results with a $p \leq 0.05$ are considered statistically significant. Statistical analyses were performed using two-tailed testing. Reported numbers indicate mean value ± standard deviation (SD) unless otherwise stated. Since all dependent variables were normally distributed (tested using Kolmogorov–Smirnow test), parametric tests were used throughout. Three separate 2 × 2 repeated measures (rm) ANOVAs with the within-subject factor STIMULATION (pain/no pain) and the between-subject factor EXPECTANCY (positive/negative) were used to investigate the effects on categorization (RTs and accuracy) and recognition performance (accuracy).

The individual categorization performance was defined as the percentage of correct classifications pooled across living and non-living objects. Mean reaction times (RT) were computed for correctly classified images (pooled across living and non-living objects) separately for each experimental condition. To quantify the recognition performance, the percentage of hits for each condition (i.e. number of remembered pictures in one condition divided by the number of presented pictures in the same condition) and the individual false alarm rate were calculated. Correlations between the individual interference effects (i.e. differences in categorization performance, mean RTs and recognition accuracy) and the questionnaire scores were tested using Pearson's correlation coefficient.

2.7 fMRI data acquisition

MR scanning was performed on a 3T MRI system (MAGNETOM Trio, Siemens, Erlangen, Germany) with a standard 32-channel head coil. A total of 42 axial slices (slice thickness, 3 mm) per volume were acquired using a gradient EPI T2*-sensitive sequence with the following parameters: repetition time (TR) 2.15 s; echo time (TE) 25 ms; flip angle 90°; field of view 222 × 222 mm. Prior to the functional scans, an individual high-resolution anatomical image was obtained for each subject using a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (slice thickness, 1 mm; TR, 2.30 s; TE, 2.98 ms; flip angle, 9°; field of view, 256 × 256 mm).

2.8 Image processing and statistical analyses

Image processing and statistical analysis of fMRI data were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm). After removing the first six volumes to compensate for T1 saturation effects, preprocessing included slice timing and realignment to the first volume. Realignment parameters were checked for excessive head movement. The anatomical volume was co-registered with the mean echo-planar image. High-resolution T1 anatomical images were then segmented into grey matter, white matter, and CSF using the 'new segment' routine implemented in SPM8. These segmented images were used to create a study-specific structural template and single-subject flow fields using the DARTEL toolbox (Ashburner, 2007) for SPM8. Single-subject contrast images were normalized to Montreal Neurological Institute (MNI) space via the template and the single-subject flow fields. Both structural and functional volumes were normalized to standard MNI space. Functional images were resampled to a voxel size of 2 × 2 × 2 mm and finally smoothed with an 8 mm Gaussian kernel with FWHM.

2.9 fMRI analysis

Data analysis was performed using the general linear model (GLM). On the subject level, the model for the categorization phase contained three regressors that coded for: (1) presentation of images alone (control), (2) presentation of images with concomitant painful stimulation (pain) and (3) an additional regressor-of-no-interest coding for the rating period after painful stimulation. Each boxcar stimulus function (modelled duration was set to 0 s) was convolved with a canonical hemodynamic response function, and 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, resulting in a t-statistic for each voxel. In a next step, two separate contrast images representing the two conditions control and pain were generated for each subject, which were

subsequently included to a second GLM. At group level, a random-effects approach was used (Friston et al., 1999), treating inter-subject variability as a random factor and including non-sphericity. Imaging data were modelled using a full factorial model with the factors STIMULATION (pain/control) and EXPECTANCY (positive/negative).

The threshold for all statistical analyses described above was set to $p \leq 0.05$, familywise-error-corrected (FWE) for multiple comparisons. As we were not interested in pain processing *per se* but in the influence of expectation on the effects of pain on visual task performance, we focused our analysis on attention and task-related areas rather than classical pain-related areas. Based on previous studies showing reduced recognition rates and neuronal activity changes in medial temporal and ventral visual areas during simultaneous painful stimulation (Bingel et al., 2007; Forkmann et al., 2013), we performed regions-of-interest (ROI) analyses using FWE small volume correction (Poldrack, 2007; Worsley et al., 1996) on the following areas: fusiform gyrus, hippocampus, anterior cingulate cortex (ACC) and inferior parietal cortex. The regions were defined anatomically using the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). In addition to these ROI analyses, we performed a whole-brain analysis ($p \leq 0.05$, FWE-corrected).

2.10 Psychophysiological interaction analysis

To further examine the modulatory mechanisms underlying possible differences due to the expectancy manipulation, two psychophysiological interaction (PPI) analyses (Friston et al., 1997) were performed. A PPI analysis reveals differences in functional connectivity between a particular seed region and all other voxels across the entire brain as a function of a psychological factor. Here, we conducted two separate PPI analyses to identify brain regions that showed differential connectivity with (1) the ACC and (2) the hippocampus during painful stimulation. The ACC (xyz = [(−2 38 8]) and hippocampus (xyz = [(−30 −36 2]) were used as seed regions because they showed a STIMULATION × EXPECTANCY interaction of neural activity, as identified by the contrast (positive expectancy$_{[pain>control]}$ > negative expectancy$_{[pain>control]}$); see Results]. Furthermore, both areas have previously been described to exert modulatory influences on visual brain areas in a visual encoding task (Bingel et al., 2007; Forkmann et al., 2013). The blood oxygenation level-dependent (BOLD) time series was extracted from the activation clusters detected in the interaction analysis (ROI analysis FWE $p = 0.05$ corrected; positive expectancy$_{[pain>control]}$ > negative expectancy$_{[pain>control]}$) for every subject individually using the first eigen time series (principal component analysis). Each PPI regressor was calculated for each subject as the element-by-element product of the mean-corrected activation of the seed region (extracted time series) and the vector coding for the psychological variable (−1 on regressor painful stimulation, 1 on regressor control stimulation, that is coding for areas with lower connectivity during painful stimulation as compared to pain-free control trials). Thus, these PPIs tested for a pain-associated modulation of the functional connectivity between (1) the left hippocampus or (2) the left ACC and any other brain region. Finally, the individual contrasts reflecting the interaction between the psychological and physiological variables (PPI regressor) were entered into a two-sample t-test. We hypothesized that functional connectivity between task-relevant areas (hippocampus and fusiform gyrus), pain-related areas (ACC) and attention-related areas (inferior parietal cortex/superior parietal cortex (IPC/SPC)) would differ between the positive and negative expectancy groups. Corrections in these regions were based on anatomically defined regions using the AAL atlas (Tzourio-Mazoyer et al., 2002).

3. Results

3.1 Behavioural results

3.1.1 Expectancy

Subjects' expectation of how pain might influence their task performance differed between groups ($t_{(40)} = 4.0$, $p < 0.001$; negative expectancy: −1.3 ± 1.3 (M ± SD), positive expectancy 0.8 ± 2) with lower expectation values for the negative expectancy group, indicating a successful expectation manipulation (see Fig. 1B). Ratings in the negative expectancy group were significantly lower than 0 ('no influence'), while ratings in the positive expectancy group did not differ from 0.

3.1.2 Categorization task

A 2 × 2 rm ANOVA for categorization accuracy revealed a main effect of STIMULATION ($F_{(1,40)} = 5.0$, $p = 0.031$) and a STIMULATION × EXPECTANCY interaction ($F_{(1,40)} = 4.31$, $p = 0.044$) but no main effect of EXPECTANCY ($F_{(1,40)} = 0.03$, n.s.). In the negative expectancy group, categorization

accuracy decreased during painful stimulation ($t_{(20)} = 3.24$, $p = 0.004$), while pain did not affect categorization accuracy in the positive expectancy group ($t_{(20)} = 0.11$, n.s., see Fig. 1C). A second 2 × 2 rm-ANOVA for RTs showed a main effect of STIMULATION ($F_{(1,40)} = 22.9$, $p < 0.001$) but no main effect of EXPECTANCY ($F_{(1,40)} = 0.001$, n.s.) and no interaction between both factors ($F_{(1,40)} = 0.23$, n.s.). *Post hoc t*-tests revealed that RTs were slower during painful trials (RT pain: 1351 ± 380 ms, control: 1210 ± 322 ms, $t_{(41)} = 4.768$, $p < 0.001$). Correlational analyses revealed a statistical trend towards a significant positive correlation between categorization accuracy (pain-control) and expectation ($r = 0.303$, $p = 0.051$, see Fig. 1D) suggesting that lower individual expectations were associated with poorer categorization accuracy during painful stimulation.

3.1.3 Surprise recognition task

The 2 × 2 rm ANOVA revealed a main effect of STIMULATION ($F_{(1,40)} = 13.3$, $p < 0.001$), indicating a poorer recognition rate for pictures paired with pain. No effect of EXPECTANCY ($F_{(1,40)} = 0.46$, n.s.) and no interaction ($F_{(1,40)} = 0.006$, n.s.) was detected. Correct rejection rate did not differ between both groups (positive expectancy group 71.4 ± 14.1; negative expectancy group: 72.1 ± 12.3, $t_{(40)} = 0.164$, n.s.).

3.1.4 Questionnaires

No significant correlations between pain-induced performance differences (categorization accuracy, recognition performance) and questionnaire scores were detected after applying Bonferroni correction for multiple comparisons.

3.2 Imaging results

3.2.1 Pain-related activity during encoding

We first identified brain areas responding to painful thermal stimulation, pooled across both groups. This analysis revealed significant activations within the well-known cerebral pain network (Apkarian et al., 2005), including the contralateral secondary somatosensory cortex/rolandic operculum, bilateral anterior insula, contralateral thalamus, as well as the medial and anterior cingulate cortex (ACC; see Table 1). Next, we were interested in brain areas, in which activation decreased during concurrent painful stimulation. Here, we detected a reduction in the bilateral anterior hippocampus and the right fusiform cortex during painful stimulation, which was independent of subjects' expectancy (Supporting Information Fig. S1 and Table 1).

3.2.2 Expectancy-dependent activity differences

The experimental induction of positive expectancy induced a higher activation in the left fusiform gyrus compared to negative expectancy (see Table 1) independent of stimulation (main effect of EXPECTANCY). The interaction analysis (positive expectancy$_{[pain>control]}$ > negative expectancy$_{[pain>control]}$) that tested for brain regions mediating the behavioural interaction effect revealed higher activations in the bilateral hippocampus (see Fig. 3B right panel visualizing the seed), rostral ACC (rACC) and right inferior parietal cortex during painful stimulation as compared to control trials for the positive expectancy group (see Table 1 and Fig. 2A and B) in contrast to the negative expectancy group. Furthermore, activity in rACC correlated with subjects' expectancy ($r = 0.4$, $p = 0.007$ Fig. 2C), indicating that lower expectations were associated with lower rACC activation during painful stimulation. The analysis of individual beta estimates in rACC showed a main effect of STIMULATION ($F_{(1,40)} = 8.03$ $p = 0.007$) as well as an interaction between STIMULATION and EXPECTANCY ($F_{(1,40)} = 13.7$, $p < 0.001$). *Post hoc t*-tests revealed a group difference between control conditions ($t_{(40)} = -3.06$, $p = 0.004$) as well as differences in activation during pain trials and control trials for the positive expectancy group ($t_{(20)} = 4.4$, $p < 0.001$).

3.2.3 PPI analyses

To explore the modulatory mechanisms underlying these expectancy-induced differential effects, we investigated changes in functional connectivity of the hippocampus and rACC depending on painful stimulation and expectancy manipulation. To this end, two PPI analyses tested for a pain-related connectivity modulation between (1) the left rACC [(−2 38 8); see Fig. 2A] or (2) the left hippocampus [(−20 −10 −24); see Table 1] and any other brain region. These analyses revealed that, only in the negative expectancy group, pain reduced functional connectivity between rACC or hippocampus and the right posterior fusiform gyrus, a region implicated in object recognition (see Fig. 3 and Table 1). The strength of connectivity between hippocampus and right posterior fusiform gyrus did not correlate with the recall accuracy during the surprise recognition

Table 1 Imaging results (BOLD activation peaks).

	Coordinates (mm)							
	Left			Right				
Region	*x*	*y*	*z*	*x*	*y*	*z*	Voxel level (*T*)	Cluster size
Pain-related neuronal activation (pain > control)								
Rolandic operculum/insula/SII				38	−18	18	9.18	191
				54	−2	8	7.22	162
Anterior insula				34	8	14	5.81	28
	−36	8	6				5.21	3
Supramarginal gyrus				54	−22	24	6.59	97
Supplementary motor area	−4	14	50				5.6	18
Thalamus				14	−10	8	5.44	6
Midcingulate cortex				8	−16	28	5.23	2
				6	14	36	5.15	2
				2	8	40	5.13	2
Anterior cingulate cortex	0	24	30				4.61*	91
				2	24	28	4.31*	96
Inferior/superior parietal cortex				20	−44	68	4.44*	42
Task-related activity disrupted by pain (control > pain) (Fig. 3)								
Fusiform gyrus				28	−28	−24	3.88*	5
Anterior hippocampus	−20	−10	−24				3.91*	49
				32	−14	−22	3.68*	10
Activity related to positive expectancy (positive expectancy > negative expectancy)								
Fusiform gyrus	−24	−74	−8				3.87*	66
Stimulation × expectancy interaction (positive expectancy$_{(pain>control)}$ > negative expectancy$_{(pain>control)}$) (Fig. 2)								
IPC/SPL				58	−54	40	3.93*	15
Anterior cingulate cortex	−2	38	8				3.82*	29
	−4	22	−8				3.70*	8
	−6	46	2				3.67*	21
				8	44	22	4.09*	29
Hippocampus	−30	−36	−2				4.13*	32
				32	−38	2	3.70*	4
PPI Hippocampus [−30 −36 2] (negative expectancy$_{(control>pain)}$ > positive expectancy$_{(control>pain)}$) (Fig. 3A)								
Fusiform cortex				28	−56	−10	4.38*	35
PPI rACC [−2 38 8] (negative expectancy$_{(control>pain)}$ > positive expectancy$_{(control>pain)}$) (Fig. 3B)								
Fusiform cortex				32	−54	−14	4.16*	15

Coordinates are denoted by *x*, *y*, *z* in mm according to the MNI-space (Montreal Neurological Institute). Strength of activation is expressed in t-scores ($df = 80$). All results are $p < 0.05$ whole-brain FWE corrected for multiple comparisons except (*), which are corrected using *a priori* regions-of-interest (see Methods). PPI = psychopysiological interaction.

task, neither for the whole sample ($r = 0.02$, $p = 0.9$) nor for the manipulated groups (positive group: $r = -0.2$, $p = 0.37$; negative group: $r = 0.28$, $p = 0.2$).

4. Discussion

This study explored the influence of expectation on the interruptive function of pain using fMRI in healthy volunteers. Expectation was successfully manipulated using verbal instructions before subjects performed a visual categorization task and a surprise recognition task. Subjects in the positively manipulated group expected no effect of pain while subjects in the negatively manipulated group expected pain to compromise their task performance. In line with our hypothesis, the expectancy manipulation led to a significantly different task performance in both groups. Categorization accuracy decreased during concurrent pain in the negative expectancy group, while no effect was observed in the positive expectancy group. These results indicate that, behaviourally, we were not able to induce better task performance through pain compared to our control condition but at least we were able to abolish the negative impact pain commonly has on task performance. These behavioural differences were accompanied by increased activity in pain-related (rACC) and task-related (hippocampus (Hampson et al., 2004)) areas during pain in the positive expectancy group

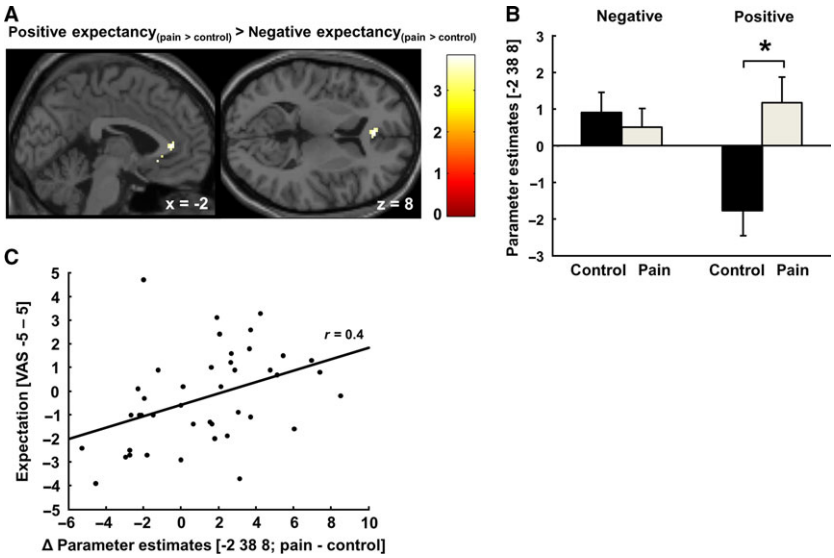

Figure 2 Positive expectancy recruits rACC during concurrent painful stimulation. (A) BOLD activations in the rACC (positive expectancy$_{[pain>control]}$ > negative expectancy$_{[pain>control]}$) overlaid on a T1-weighted image (for details see Table 1). The image is thresholded at $p < 0.001$ uncorrected for visualization purposes. (B) Parameter estimates of pain-related BOLD responses for the activation peak in the left rACC plotted for visualization purposes (extracted from the peak voxel of activation – for details see Table 1). Error bars indicate standard errors of the mean (SEM). *$p < 0.05$. (C) For visualization purposes: Differences in rACC activity (pain–control) varied depending on subjective expectancy of how pain would influence task performance.

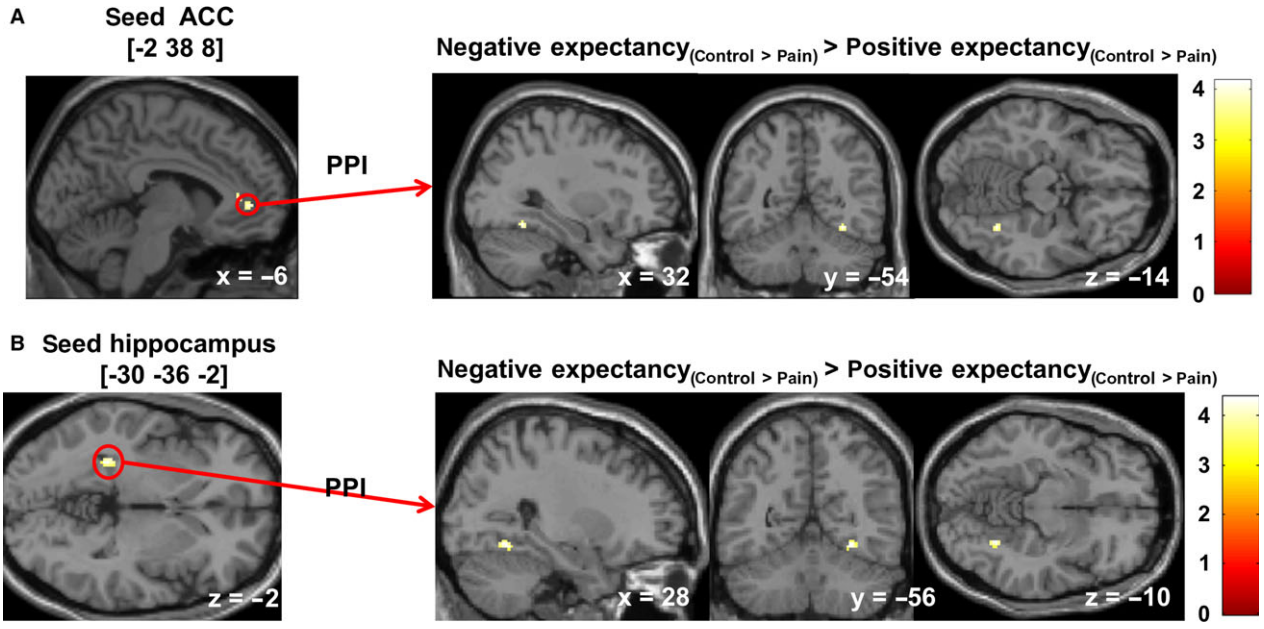

Figure 3 Expectancy and painful stimulation modulate functional coupling between rACC, hippocampus and visual processing areas. (A) The left rACC was defined as the 'seed' (peak coordinate *xyz* = −2 38 8, cluster size: 29 voxel; activation cluster identified in the interaction analysis (positive expectancy$_{[pain>control]}$ > negative expectancy$_{[pain>control]}$)). A PPI (psychophysiological interaction) analysis revealed a reduction in functional connectivity between the left rACC and right posterior fusiform gyrus during painful stimulation for negative expectancy compared to positive expectancy. (B) Similarly, the left hippocampus ('seed'; cluster around peak coordinate *xyz* = −30 −36 −2 from the interaction analysis, cluster size: 32 voxel, see Results) showed a reduction in functional connectivity between the left hippocampus and the right posterior fusiform gyrus during painful stimulation for negative expectancy compared to positive expectancy. For visualization purposes, results are overlaid on a T1-weighted image and thresholded at $p < 0.001$ uncorrected.

as compared to the negative group. Activation differences in the rACC correlated with individual differences in recognition accuracy. Furthermore, painful stimulation impaired functional connectivity between pain-related (rACC), encoding-related (hippocampus) and task-related (posterior fusiform gyrus) areas in the negative expectancy group compared to the positive expectancy group.

4.1 Expectancy modulates visual categorization accuracy

The present study replicates findings from our previous study (Forkmann et al., 2013) showing slower categorization responses and decreased recognition accuracy for pictures paired with painful heat stimuli compared to those without concomitant stimulation. Importantly, we successfully manipulated subjects' expectation about how pain influences cognitive functioning as indicated by the difference in expectation ratings between both groups. In a previous study, we assessed participants' expectations regarding the effect of pain on task performance without any experimental expectancy manipulation before a visual task was performed with or without concomitant painful stimulation. We found that participants generally expected pain to have a negative effect on their task performance when no prior information was provided (Forkmann et al., 2016; Sinke et al., 2015). This 'no manipulation' expectation regarding the effect of pain on task performance assessed in our previous study was comparable to that observed in the negative expectation group, supporting the notion that negative expectations represent the 'default' expectation regarding pain–cognition interaction. Importantly, our verbal instruction to induce positive expectations was able to override this negative 'default' expectation. As hypothesized, the induced expectation affected the interruptive function of pain as indicated by the stimulation x manipulation interaction in the categorization task. Pain impaired categorization accuracy in the negative expectancy group whereas the interruptive effect of pain was absent in the positive expectancy group. While expectancy modulated the interruptive effect of pain on categorization accuracy, it had no effect on the surprise memory task. This finding is rather unexpected and raises the question how persistent these effects are and whether secondary processes (such as subsequent memory of the images) are affected at all. We speculate that the expectation manipulation only affects those tasks that the participants knew of in advance. We are aware that a direct assessment of the individual expectancy manipulation inevitably bears the risk of unblinding the research question, but the chance of unblinding was reduced by masking the assessment of expectancy with other questions assessing the subjects' current state. Nevertheless, we consider it important to assess individual expectations to capture inter-individual differences in expectations and beliefs that occur despite (or in response) to our standardized instructions.

Our findings are well in line with a recent study by Boselie et al. (2014), showing that the disruptive effect of pain on task performance in an operation-span task was successfully prevented by experimentally induced optimism, an implicit or unspecific expectation of something positive to happen (Scheier and Carver, 1985). Similar effects of implicit expectations on behavioural performance have been reported in the stereotype-thread literature (Kit et al., 2008). Activating stereotypes, for instance by emphasizing group membership, can influence task performance. Mathematical task performance of female participants decreased after they have been reminded of the stereotype of lower mathematical skills in women, which induced the expectation to perform worse (Spencer et al., 1999). The mere fact that the interruptive function of pain is prone to expectation manipulations suggests that the inherent ability of pain to attract attention and interfere with cognitive functioning (Crombez et al., 1996) might, at least in part, be due to the presumption that pain compromises cognitive performance. This would mean that pain does not directly influence task-related/sensory areas but that there is a rather indirect, cognitively mediated pathway (i.e. changes in functional connectivity between task-related, pain-related and memory-related areas) responsible for the detrimental effects of pain, which could offer an interesting route of intervention to target the cognitive consequences of acute and chronic pain. An interesting and clinically relevant question for further research that could not be answered in the present study is how long the effects of positive expectation manipulations persist before individuals return to their (mainly negative) default expectation.

4.2 Expectancy modulates functional connectivity between pain-related and task-related areas

The induction of positive and negative expectation differentially modulated neural activity and functional connectivity in pain-relevant and

task-relevant brain regions in response to pain. Painful stimulation reduced activation in the bilateral anterior hippocampus and the right posterior fusiform gyrus irrespective of expectation, which replicates our previous findings (Forkmann et al., 2013). This reduced activation of visual and encoding-relevant brain regions likely explains the pain-induced impairment in recognition performance.

With respect to our main objective, the behavioural interaction between painful stimulation and expectancy was accompanied by higher activity in the inferior parietal cortex, hippocampus and rACC during pain in the positive expectancy group compared to the negative expectancy group. This finding supports the notion that positive expectation prevented the interruptive function of pain through an altered recruitment of task-related (hippocampus) and attention-related (IPC) areas. Thus, increasing task-related and attention-related brain activation by manipulating expectations about pain might be an effective way to overcome the detrimental effects of pain on cognition. Moreover, the PPI analyses revealed decreased coupling between the rACC and the posterior fusiform gyrus as well as the hippocampus and the posterior fusiform gyrus during painful stimulation in subjects expecting pain to impair their performance compared to those who expected pain to improve their performance. Expecting pain to decrease performance induced less functional connectivity between pain- and task-related areas as well as visual processing and memory-related areas. Two previous studies of our own group have reported a pain-induced reduction of functional connectivity between similar brain regions (Bingel et al., 2007; Forkmann et al., 2013). While Bingel et al. (2007) observed reduced functional connectivity between visual processing areas (i.e. LOC) and the rACC that is known to be implicated in pain modulation and attention, Forkmann et al. (2013) reported impaired functional connectivity between visual processing regions (i.e. fusiform gyrus) and the hippocampus, a region implicated in encoding and memory. Here, we extend these findings by showing that the pain-induced connectivity changes between rACC and task-related areas (such as fusiform cortex), as well as the connectivity changes between different task-related areas (i.e. hippocampus, fusiform gyrus) were modulated by the subjects' expectation. This finding suggests that it is not the nociceptive stimulus *per se* but the default assumption that pain impairs performance that leads to the observed modulatory functional connectivity. In contrast, the expectation that pain improves task performance was accompanied by higher activity in rACC and an increased communication between pain-related and task-related areas during painful stimulation, thereby abolishing the negative effects of pain. This study did not allow to identify the exact role of the hippocampus, rACC and posterior fusiform gyrus. However, our data imply a cognitively mediated neural pathway including pain-related (rACC), task-related (posterior fusiform gyrus) and memory-related areas (hippocampus), that is dependent on expectations as our expectation manipulation was able to change this functional coupling. The rACC is ideally suited to implement the effect of cognitive processes (such as expectations on the perception of pain) as it contains a subdivision related to cognitive processing and a subdivision related to emotional processing (Bush et al., 2000). We show that a verbal instruction that aimed at changing expectations altered neural activation and communication in and between task-related brain areas. When extracting parameter estimates of rACC activation, we found that the interaction between stimulation and expectation manipulation was due to a difference between control conditions rather than painful conditions (see Fig. 2B). Here, it has to be pointed out that our manipulation was likely to induce a relative effect between the pain and control condition in both groups. The explicit information that pain would impair or boost performance also involves an implicit statement about the control condition, that is the absence of pain leads to better or worse task performance respectively. This relative rather than absolute manipulation might have induced activation differences in the control condition between both groups as found in the rACC. We believe that this differential effect on rACC in the control condition is attributable to the manipulation, which underscores the impact of expectations, explicit or implicit, on task performance.

4.3 Clinical implications

Our data demonstrate that the disruptive effect of pain on cognitive performance (Grisart and Plaghki, 1999; Grisart et al., 2007; Moriarty et al., 2011; Oosterman et al., 2012) is not inevitable. The effect of pain on cognition is rather modulated by an individuals' expectation, which is sensitive to verbal instructions. The findings provided here might have important implications for patients suffering from chronic pain disorders, as cognitive impairment is known to crucially contribute to the overall suffering of pain patients and the economic consequences

associated with decreased work productivity (Blyth et al., 2003). Our findings suggest that the physiological effects of pain and negative expectations can be effectively addressed in healthy subjects using positive instructions. The experience of long-standing pain and cognitive impairment in pain patients induces strong negative expectations, which in turn might enhance the impairing function of pain. These results offer the possibility for a therapeutic intervention in targeting these negative expectations and thereby counteracting the negative influence of pain on cognition in chronic pain patients.

5. Conclusion

Here, we show that verbally induced expectations influence the interruptive function of pain. Neutralizing the (genuine) assumption that pain impairs cognitive functioning can abolish its detrimental effects on task performance. These behavioural changes are accompanied by activity changes in pain-, attention- and task-relevant areas as well as changes in functional connectivity between rACC and posterior fusiform gyrus as well as hippocampus and posterior fusiform gyrus. The relevance of this observation in clinical pain states warrants further investigation.

Author contributions

CS was involved in designing the experiment, acquisition and analysis and interpretation of data and writing the manuscript. UB was involved in conception and designing the experiment, interpreting the data and writing the manuscript. KF was involved in designing the experiment, interpretation of data and writing the manuscript. KS was involved in acquiring data, interpretation of data and writing the manuscript. All authors approved the final manuscript for publication.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Concurrent painful stimulation reduced anterior hippocampal activity during encoding.

