

Empathy for pain-related dorsolateral prefrontal activity is modulated by angry face perception

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Abstract Empathy, i.e., the ability to perceive and share another person's affective state, is associated with activity in a complex neural network, including the anterior insula, the anterior and mid-cingulate cortex, and the lateral prefrontal cortex. Here, we were interested in the question how facial emotions influence the activation of the 'pain network'. In the present study, we used functional magnetic resonance imaging to investigate the neuronal correlates of empathy for pain and its interaction with emotional face recognition in 20 healthy subjects. We identified various brain regions commonly associated with empathy for pain, including the right mid-cingulate cortex, the left anterior insula (AI), and the left dorsolateral prefrontal cortex (dlPFC), with an increased neuronal response in the left dlPFC after the presentation of angry faces. Furthermore, a negative correlation between psychological measures of alexithymia and empathy for pain-related brain activity was observed in the left AI. The dlPFC is an important brain region involved in cognitive reappraisal or in 'top-down' control of the limbic system. Our findings could therefore reflect a regulatory response associated with distancing

from negatively valenced stimuli. Moreover, our results underline the involvement of the AI in empathy for pain responses and their relationship to alexithymia.

Keywords Empathy · Emotion · Anterior insula · Dorsolateral prefrontal cortex · Functional magnetic resonance imaging

Introduction

Empathy, i.e., the ability to share another's internal feelings (Walter 2012), is a core element of our everyday communication and social interaction and therefore essential for successful navigation in social environments (Eisenberg and Strayer 1987). From a theoretical point of view, empathy is a complex psychological mechanism encompassing affective behaviour, affective experience and isomorphy, perspective taking, and self–other distinction. It needs to be distinguished, on a conceptual level, from emotional mimicry, emotional contagion, personal distress, and sympathy (Gonzalez-Liencre et al. 2013). In this context, it is important to differentiate between affective empathy as outlined above and cognitive empathy, i.e., the ability to understand another's mental states in terms of thoughts, desires, or intentions (Shamay-Tsoory et al. 2009). According to Batson (2009), empathy is the 'experiencing of an affective or sensory state similar to that shown by a perceived individual' while maintaining the self–other distinction (Singer and Lamm 2009). This complex psychological mechanism allows us to predict and understand feelings, motivations, and actions of another (Bernhardt and Singer 2012; Gonzalez-Liencre et al. 2013). Based on the induction of the empathic response, two distinct forms of empathy are believed to exist that share (at least partly) the same

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neuronal representations. Affective–perceptual empathy describes a passive empathic response without any conscious intellectual examination of another person’s feeling, whereas ‘cognitive–evaluative’ empathy describes an explicit form of examination of another person’s feeling (Fan et al. 2011).

Numerous functional magnetic resonance imaging (fMRI) studies have investigated the neuronal correlates of empathy in humans. Key regions associated with affective empathy are the bilateral anterior insula, the mid-cingulate cortex, the anterior cingulate cortex, the orbitofrontal cortex, the supplementary motor area, and the dorsomedial thalamus (Fan et al. 2011). Regarding the neuronal response associated with empathy for pain, Lamm et al. (2011) showed in a recent meta-analysis of fMRI-based studies that the ventral and dorsal subdivisions of bilateral anterior insula (AI), the mid-cingulate cortex, and the pregenual anterior cingulate cortex form a ‘core’ neuronal network. This empathy network shows a great overlap with the neural network activated by first-hand experience of pain (Lamm et al. 2011). Part of the pain matrix is the primary and secondary somatosensory cortices, anterior cingulate cortex and mid-cingulate cortex as part of the prefrontal cortex, thalamus, (anterior) insula, and basal ganglia (Duerden and Albanese 2013). A potential explanation of this convergence arises from the ‘shared representations’ approach (Lamm et al. 2011; Bernhardt and Singer 2012), suggesting that ‘neural circuits involved in the personal experience of an emotion underpin the understanding and sharing of the same emotion perceived in others’ (Lamm et al. 2011). Despite the already mentioned overlap of the empathic network and the pain matrix, it is possible to disentangle these two processes at a neuronal level (Zaki et al. 2007; Jabbi et al. 2008; Lamm et al. 2011). Recent research suggests a posterior-to-anterior gradient within the insular cortex. Following this model, first-hand experience of pain is related to an activation of the posterior subdivisions associated with the sensory dimensions of nociception, whereas the AI integrates affective–emotional representations and interoception in both conditions, i.e., empathy for pain and first-hand experience of pain (Lamm et al. 2011). Empathy-related activation of the cingulate cortex—a region closely connected to the insular cortex (Kelly et al. 2009)—is commonly observed in affective–motivational subdivisions, whereas the first-hand experience of pain shows an extended activation pattern including brain regions associated with action control (Lamm et al. 2011). In this context, it should be noted that the anterior and mid-cingulate cortex are part of the so-called cortical mid-line structures, a set of brain regions commonly associated with self-referential processes (Northoff et al. 2006). The extended activation of these brain regions during first-hand experience of pain could therefore reflect the distinction between the

self-relevant and vicarious experience of pain (Lamm et al. 2011). Of note, the conception that empathy for pain and pain experience shares (at least partly) the same neuronal network has been challenged and refined by recent work (Zaki et al. 2016) as well as criticized for relying on reverse inference (Poldrack 2006).

In contrast to the wealth of work on empathy for pain in general, there is much less research on the impact of facial expressions of emotions on the processing of painful stimuli. For example, a painful stimulus that is associated with a counter-intuitive smiling face is likely to produce a different neuronal signature compared to painful stimuli combined with the expression of a negative emotion.

This could be highly relevant, particularly when considering the role of the dorsolateral prefrontal cortex (dlPFC) in the modulation of emotional responses. For example, Ray and Zald (2012) have argued that the dlPFC is involved in cognitive reappraisal, that is, modifying an emotional response according to one’s cognitive reinterpretation of (emotional) information (Ochsner and Gross 2005). It could therefore be that the visible association of negative facial expressions such as anger or pain with a painful stimulus recruits additional cortical regions such as the dlPFC, which has hitherto not been considered to be part of the pain matrix, but may play a role as regulatory structure (Moriguchi et al. 2007; Ochsner et al. 2008). Another explanation for the above-mentioned relationship between emotion processing and empathy could involve the concept of alexithymia, i.e., the reduced awareness of own and others’ feelings in combination with difficulties in identifying and describing feelings (Ernst et al. 2013). Accordingly, it is plausible to assume that alexithymic subjects show a weaker emotional response and as a consequence a reduced empathic response related to pain. In addition, various brain imaging studies showed a reduced activation of the AI related to alexithymia (Ernst et al. 2013), an important structure for emotion processing and empathy (for pain; Lamm et al. 2011).

Here, we sought to analyse the neural responses to an empathy-for-pain task preceded by the presentation of different emotional facial expressions (angry, happy, painful, and neutral). We hypothesized that the contrast [empathy for pain > no pain] would show reliable activation of the pain matrix in general, i.e., the AI, lateral prefrontal cortex, anterior and/or mid-cingulate cortex. More specifically, we predicted that emotional facial expressions—especially angry and painful facial expressions—would increase the activation of the pain matrix and possibly lead to an additional recruitment of dlPFC activity, a known top-down regulator of empathic responses (Decety 2011). In addition to previous research in this field (see Han et al. 2009; for a related experimental paradigm investigating the interaction between emotion and empathy for pain), we used a

sequential experimental paradigm (instead of simultaneous presentation) with an emotional pictorial stimulus directly preceding the pain/no pain condition. Our aim was to evoke an affective state in the observer and the investigation of its influence on subsequent empathy trials. Furthermore, since previous research demonstrated that painful facial expression is sometimes misidentified as disgust, embarrassment, or fear (but not as anger or sadness) (Kappesser and Williams 2002), we included angry faces as an additional emotional condition with negative valence. Happy facial expressions were included based on Han et al. (2009) observations of a decreased activity in the pain matrix, mainly the secondary somatosensory cortex, related to conflicting trials, e.g., happy facial expression and painful situation. Moreover, we were interested in examining possible correlations between empathy for pain-related activity in the AI and alexithymia as measured by the German version of the Toronto Alexithymia Scale (TAS-20). Following an exploratory approach (Bender et al. 2007), the TAS-20 scores were correlated with the signal change derived from the AI (Bird et al. 2010).

Materials and methods

Subjects

The study was approved by the ethics committee of the Medical Faculty of the Ruhr-University Bochum, Germany. After a detailed explanation of the study, all subjects gave written informed consent.

Twenty healthy subjects with no psychiatric, neurological, or other medical illnesses (all male, average age 27.0 ± 5.08 years, range 19–37 years, 18 right-handed) were enrolled in the study (Table 1). All subjects completed various neuropsychological tests, including the interpersonal reactivity index (IRI; Davis 1980) as a measure of empathic abilities, the Toronto Alexithymia Scale (TAS-20; Bagby et al. 1994) for the assessment of alexithymia, and the NEO-FFI (Borkenau and Ostendorf 1993) for the identification of personality traits according to the five-factor model.

Behavioural and neuropsychological data

The behavioural data (picture ratings regarding the emotional content) were extracted using perl (www.perl.org). Further analyses regarding behavioural data were carried out using IBM SPSS statistics for windows, version 20.0 (IBM Corp., Armonk, NY, USA). After the fMRI experiment, all participants had to rate each picture used in the paradigm regarding all facial emotional expressions, i.e., angry, happy, painful, and neutral. As a control question, subjects had to identify the gender of the shown face.

Table 1 Characteristics of healthy subjects ($n = 20$)

| | |
|--|-----------------------|
| Age (years; \pm SD) | 27.0 (\pm 5.08) |
| Sex (male/female) | 20/0 |
| Handedness (right/left) | 18/2 |
| Education years (mean; \pm SD) | 17.75 (\pm 2.46) |
| Intelligence score [MWT-B] (mean; \pm SD) ^a | 124.29 (\pm 11.18) |
| BDI score (mean; \pm SD) ^b | 3.33 (\pm 5.46) |
| TAS-20 ^b | |
| Difficulties identifying feelings | 10.89 (\pm 3.45) |
| Difficulties describing feelings | 10.22 (\pm 3.10) |
| Externally oriented thinking | 18.06 (\pm 5.35) |
| IRI ^b | |
| Perspective taking | 18.78 (\pm 5.76) |
| Fantasy | 14.83 (\pm 5.40) |
| Empathic concern | 17.44 (\pm 4.29) |
| Personal distress | 9.78 (\pm 3.96) |
| NEO-FFI ^b | |
| Neuroticism | 1.27 (\pm 0.62) |
| Extraversion | 2.54 (\pm 0.47) |
| Openness to experience | 2.64 (\pm 0.47) |
| Agreeableness | 2.53 (\pm 0.54) |
| Conscientiousness | 2.88 (\pm 0.65) |

BDI Beck depression inventory, *TAS-20* Toronto alexithymia scale, *IRI* interpersonal reactivity index, *MWT-B* verbal intelligence test [Mehrfachwahl-Wortschatz-Intelligenztest], *NEO-FFI* NEO five-factor inventory, *SD* standard deviation

^a $n = 17$

^b $n = 18$

Experimental paradigm

The applied functional imaging paradigm is a modified version of an established empathy for pain task (Lamm et al. 2007). Briefly, two picture stimuli depicting a painful or a non-painful situation were presented for 3 s. The painful stimulation conditions [pain] showed a needle penetrating another person's skin of the right hand, whereas in the non-painful conditions [no pain] a Q-tip touching another person's hand was presented. These two conditions were directly preceded by the presentation of emotional facial expressions [neutral, happy, painful, and angry] and a blank screen as an additional control condition [no emotion]. The duration of the emotion period was set to 3 s. All possible combinations between the emotional facial expression and the painful (and non-painful) stimulation, i.e., angry face followed by a painful situation, happy face followed by a non-painful situation, were presented in equal numbers, resulting in 10 conditions. All trials were separated by a jittered inter-trial interval of 3–6 s. In total, 60 trials were presented per run, 30 in the painful stimulation condition and 30 in the non-painful condition. Each emotional facial

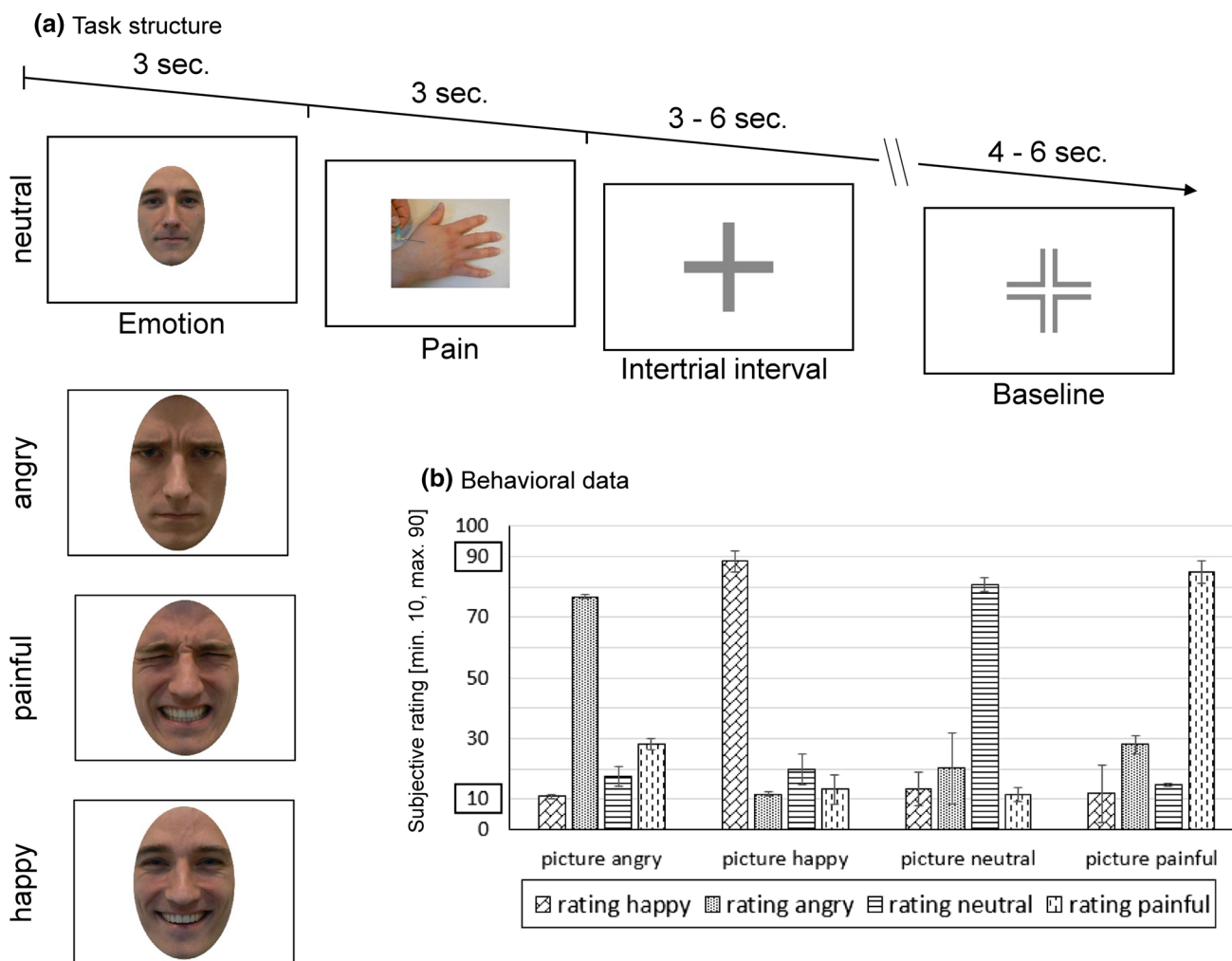


Fig. 1 **a** Design and schematic structure of the applied fMRI paradigm. **b** Behavioural data: picture ratings regarding the emotional content in $n = 20$ subjects. Error bar represents SEM

expression and [no emotion] condition were presented 12 times, i.e., each emotion was presented 6 times in the painful and non-painful condition. Six different faces were presented per emotion, i.e., each emotional facial expression was presented twice. In addition, 10 clearly distinguishable baseline events of 4–6 s were presented. In total, the experiment consists of 4 runs with a total duration of approximately 40 min. The experimental paradigm described above was presented in run 1 and 3, whereas in the remaining scanning runs 2 and 4 all subjects had to complete a similar task, where non-European faces were presented to the subjects (not part of the present analysis). All subjects were instructed to recognize the emotional expression and to empathize, i.e., share the emotional feeling of the person in the painful or the non-painful situation. At the end of each scanning run, the ability to empathize was assessed using a visual analogue scale. To avoid a possible gender effect, only pictures showing male persons and their

emotional facial expressions were presented. Furthermore, the study population was restricted to male participants (a brief description of the used paradigm is given in Fig. 1a).

The pictorial stimuli (i.e. facial emotional expressions and pain/no pain) were presented separately [in contrast to the simultaneous presentation by Han et al. (2009)] since we aimed to induce an affective state in the observer and to measure how these affective states modulate the empathic response. Happy, neutral, and painful emotional facial expressions were chosen in line with previous research (Han et al. 2009). Angry faces were included as an additional emotion with negative valence because of the previously observed misidentification of pain for other emotions, especially disgust, embarrassment, and fear (Kappesser and Williams 2002).

All pictorial stimuli were generated in our in-house photographic studio. Briefly, a cohort of male volunteers was instructed to present the facial emotional expression of

interest and photographed. After a short quality check, all pictures were rated according to their emotional content by an independent group of subjects ($n = 15$) and only unambiguous pictorial stimuli were used in the experiment. In addition, all subjects participating in the fMRI study completed a post hoc rating as shown in Fig. 1.

The experiment was presented via MRI-compatible LCD-goggles (Resonance Technology Inc., Los Angeles, CA, USA) using the ‘Presentation’ software package (Neurobehavioral Systems Inc., Albany, CA, USA).

fMRI data acquisition and analysis

Functional data were collected using a 3-Tesla whole-body MRI system (Philips Achieva 3.0T TX) equipped with a 32-channel Philips SENSE head coil. 32 T2*-weighted echo-planar (EPI) images per volume with blood-oxygen level dependent (BOLD) contrast were obtained using a sensitivity encoded single-shot echo-planar imaging protocol (SENSE-sshEPI; matrix $80 \times 80 \text{ mm}^2$, reconstructed to $112 \times 112 \text{ mm}^2$, field-of-view $220 \times 220 \text{ mm}^2$, in-plane resolution $2.75 \times 2.75 \text{ mm}^2$, slice thickness 3 mm with 1 mm gap, reconstructed to a final voxel size of $1.96 \times 1.96 \times 3 \text{ mm}^3$, TR = 2000 ms, TE = 30 ms, flip angle $\alpha = 90^\circ$, SENSE factor $R_{AP} = 2.0$). The slices were acquired in interleaved order parallel to the bi-commissural plane and provided whole-brain coverage. Subjects had to complete four scanning runs with 335 volumes per run. The first five volumes were discarded due to saturation effects. Prior to the functional scanning session, a high-resolution T1-weighted anatomical gradient echo scan was acquired for each subject (3D TFE; matrix $300 \times 235 \text{ mm}^2$, reconstructed to $320 \times 320 \text{ mm}^2$, field-of-view $240 \times 188.8 \times 192 \text{ mm}^3$, in-plane resolution $0.8 \times 0.8 \text{ mm}^2$, slice thickness 0.8 mm, reconstructed to a final voxel size of $0.75 \times 0.75 \times 0.8 \text{ mm}^3$). In total, 240 slices in transverse orientation were acquired. TR = 10 ms, TE = 4.6 ms, flip angle $\alpha = 8^\circ$, SENSE factor $R_{RL} = 2.5$ and $R_{FH} = 2.0$).

The functional data were preprocessed and statistically analysed using SPM8 (Wellcome Department of Cognitive Neuroscience, University College London, UK; <http://www.fil.ion.ucl.ac.uk>) and MATLAB 7.11 (The MathWorks Inc, Natick, MA, USA). After temporal correction and correction for between-scan motion artefacts by realignment to the first volume, the anatomical scan was co-registered to a mean functional image. The normalization was generated by warping the subject’s anatomical T1-weighted scan on the T1 template provided by SPM8 (MNI stereotactic space) and applying these parameters to all functional images. The images were re-sampled to a final voxel size of $2 \times 2 \times 2 \text{ mm}^3$ and smoothed with

an isotropic 8-mm full-width half-maximum Gaussian kernel. The time-series fMRI data were filtered to eliminate low-frequency signal drifts using a high-pass filter (cut-off 100 s).

In line with previous research (Lamm et al. 2007), we focused our analysis on the pain (and no pain) perception period. Since we aimed to investigate the modulation of pain perception by emotional face processing, the pain perception was categorized according to the preceding emotional face resulting in ten experimental conditions, i.e., the conditions [no emotion+pain], [neutral+pain], [happy+pain], [anger+pain], [painful+pain], [no emotion+no pain], [neutral+no pain], [happy+no pain], [anger+no pain], [painful+no pain], and [baseline] were modelled as regressors on the single-subject level. The beginning of the pain/no pain period was used as onset for event-related design specification. In addition, the realignment parameters were entered as regressors of no interest in the design matrix. A statistical model for each subject was calculated by convolving a haemodynamic response function with the above-mentioned design (Friston et al. 1994). All further statistical analyses followed the general linear model approach (Friston et al. 1998). For visualization of brain regions associated with pain processing, the contrast ‘positive effect of pain’, i.e., [pain > no pain] collapsed over all emotions and the [no emotion] condition, was calculated using the ‘full factorial’ option implemented in SPM8 and displayed at $p[\text{uncorrected}] < 0.001$ for an extent $k > 10$ voxel. Only activations surviving FWE correction on a cluster level were considered as significant. In regions with a clear a priori hypothesis [left dlPFC, left anterior insula(LAI)], small volume correction was applied using a sphere-shaped ROI with 5-mm radius. We concentrated all further analyses on brain regions typically involved in empathy for pain and activated in the contrast ‘positive effect of pain’, i.e., the right mid-cingulate cortex, the left dlPFC, and the LAI. Percent signal changes for the above-mentioned regions and conditions were extracted using the ‘MarsBar’ toolbox (<http://marsbar.sourceforge.net/>) for SPM8 (Brett et al. 2002). Anatomical locations of the peak voxel were labelled using the WFU PickAtlas (Maldjian et al. 2003) and by visual inspection.

All further statistical analyses (repeated measures ANOVA, t tests for dependent samples, Pearson correlations) were calculated using IBM SPSS statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). We correlated the percent signal change for the conditions [painful facial expression+pain] and [angry facial expression+pain] with the TAS-20 (3 subscales) and the NEO-FFI (5 subscales). A correction for multiple comparisons was not performed. In total, 16 correlations were calculated.

Results

Behavioural data

20 subjects had to identify the emotional content, i.e., neutral, happy, angry, and painful, of the presented facial expressions using a visual analogue scale (minimum: 10, maximum: 90). As a control question, the gender of the depicted person had to be identified.

All stimuli used in the present study were identified correctly by the subjects (one-way ANOVA and post hoc Tukey HSD test: (1) angry picture: $F_{3,20} = 339.96$, $p < 0.001$; post hoc Tukey HSD: angry versus happy: mean difference (MD) 65.0, $p < 0.001$; angry versus neutral: MD 56.58, $p < 0.001$; angry versus pain MD 48.79, $p < 0.001$; (2) happy picture: $F_{3,20} = 2402.79$, $p < 0.001$; post hoc Tukey HSD: happy versus angry: MD 77.56, $p < 0.001$; happy versus neutral: MD 75.0, $p < 0.001$; happy versus pain MD 76.56, $p < 0.001$; (3) painful picture: $F_{3,20} = 256.46$, $p < 0.001$; post hoc Tukey HSD: pain versus angry: MD 56.72, $p < 0.001$; pain versus happy: MD 71.78, $p < 0.001$; pain versus neutral MD 73.53, $p < 0.001$; (4) neutral picture: $F_{3,20} = 135.98$, $p < 0.001$; post hoc Tukey HSD: neutral versus angry: MD 63.20, $p < 0.001$; neutral versus happy: MD 60.94, $p < 0.001$; neutral versus pain MD 66.08, $p < 0.001$. Picture ratings: neutral: 80.83; angry: 76.78; happy: 88.49; painful: 84.98; gender 88.76) (Fig. 1b).

Functional imaging data

We first investigated the activation pattern associated with empathy for pain in general. The contrast ‘positive effect of pain’ revealed activations in regions commonly associated with empathy for pain like, for instance, the right mid-cingulate cortex, the left dIPFC, the LAI, and the left anterior cingulate cortex (Table 2). Based on the functional localizer approach, we focused all further analyses on three main regions of interest. Therefore, the left dIPFC/BA9 (MNI $-50, 2, 34$), the right mid-cingulate cortex (MNI $6, -4, 32$), and the LAI (MNI $-30, 26, 10$) were used for percent signal change extraction.

Using a repeated measures 2 by 5 ANOVA (within-subject factor ‘pain’ [painful, non-painful] and ‘facial emotional expression’ [neutral, happy, angry, painful, no emotion]) in SPSS 20.0, we were able to detect a significant main effect of ‘pain’ in the left dIPFC/BA9 ($F_{1,19} = 11.236$; $p = 0.003$), the right mid-cingulate cortex ($F_{1,19} = 15.376$; $p = 0.001$), and the LAI ($F_{1,19} = 5.657$; $p = 0.028$). A significant main effect of ‘emotion’ was observed in the LAI ($F_{3,17} = 4.014$; $p = 0.019$). In addition, a significant interaction between pain and emotion was only detected in the left dIPFC/BA9 ($F_{3,17} = 6.514$; $p = 0.003$).

More fine-grained analyses using *t* tests for paired samples (2-sided) revealed that in the left dIPFC/BA9 a significant differentiation between the conditions

Table 2 Activations in response to the contrast [positive effect of pain], i.e., pain > no pain collapsed over all conditions in $n = 20$

| Region | Hemisphere (left/right) | Coordinates (MNI) | Extent (voxel) | <i>t</i> value | <i>z</i> value |
|---|-------------------------|-------------------|----------------|----------------|----------------|
| AI ^a | Left | $-30, 26, 10$ | 42 | 3.35 | 3.30 |
| Fusiform gyrus | Left | $-30, -64, -6$ | 239 | 4.31 | 4.21 |
| Middle temporal gyrus (BA37) | Left | $-46, -66, 0$ | | 4.22 | 4.12 |
| Inferior temporal gyrus (BA37) ^b | Right | $54, -60, -12$ | 130 | 4.46 | 4.35 |
| Pregenua ACC | Left | $-10, 38, 26$ | 195 | 4.33 | 4.22 |
| Pregenua ACC | Left | $-12, 52, 22$ | | 4.40 | 4.29 |
| Mid-cingulate cortex (BA24) ^c | Right | $6, -4, 32$ | 105 | 4.49 | 4.37 |
| Middle occipital gyrus | Left | $-32, -94, 0$ | 371 | 4.97 | 4.81 |
| Middle occipital gyrus | Right | $26, -84, 4$ | 370 | 5.18 | 5.01 |
| Dorsal ACC | Right | $10, 26, 32$ | 166 | 3.93 | 3.85 |
| Dorsal ACC | Right | $12, 18, 44$ | | 4.45 | 4.34 |
| Dorsolateral PFC (BA9) ^a | Left | $-50, 2, 34$ | 96 | 4.17 | 4.08 |
| Dorsolateral PFC ^a | Left | $-40, 42, 18$ | 57 | 3.77 | 3.70 |

Initial threshold $p[\text{uncorr.}] < 0.001$ for $k > 10$ voxel. All activations survived FWE correction on cluster level with $p[\text{FWE}] < 0.05$

ACC anterior cingulate cortex, BA Brodmann area, PFC prefrontal cortex

^a $p[\text{FWE}] < 0.05$ after small volume correction (SVC) with 5-mm radius

^b Extending to the right fusiform gyrus

^c Extending to the left precentral gyrus

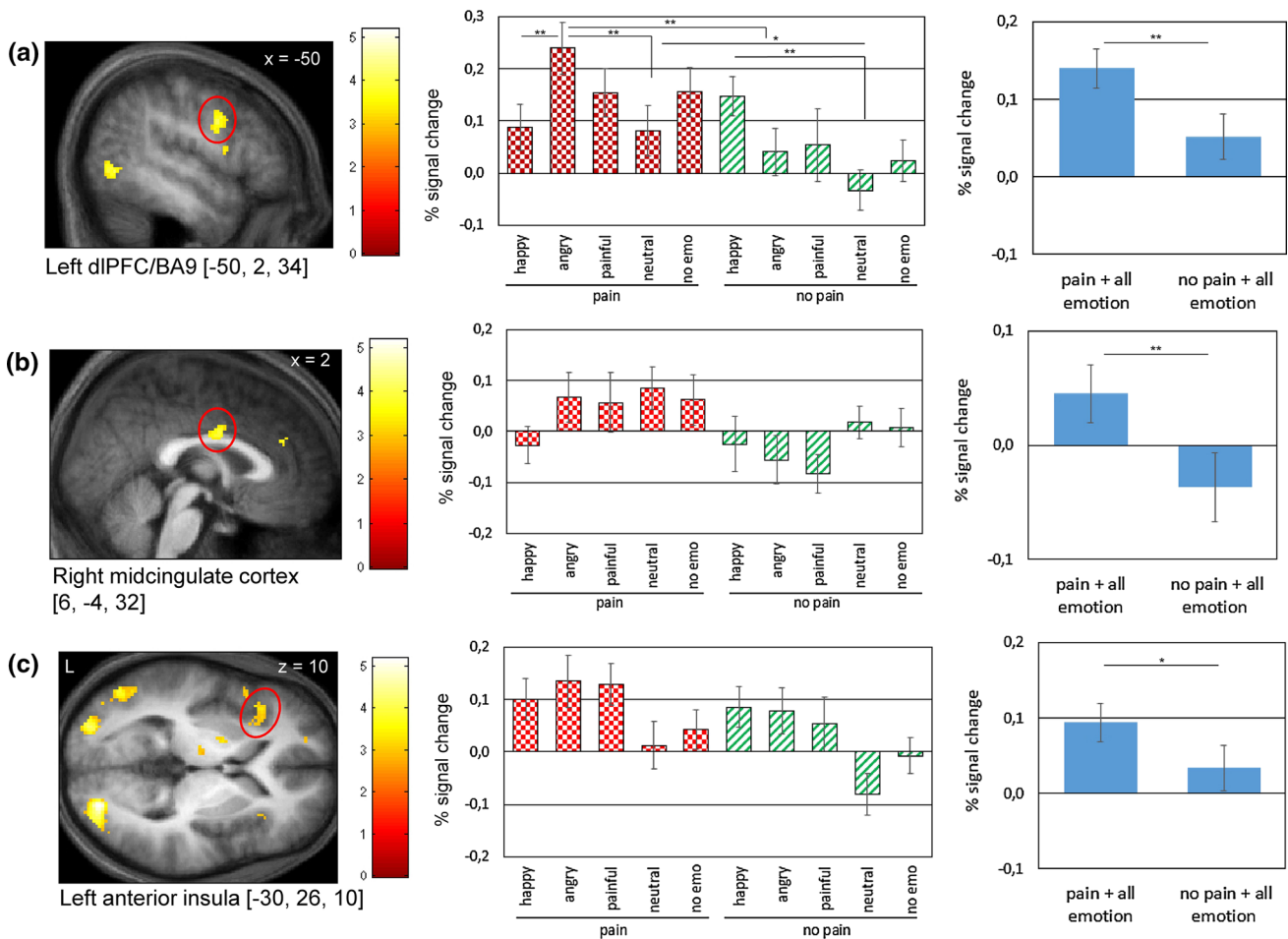


Fig. 2 Activations and percent signal change derived from the t-contrast ‘positive effect of pain’, i.e., ‘pain > no pain’ collapsed over all emotions ($n = 20$). **a–b** Statistical parametric maps for the above-mentioned contrast and percent signal change for the [pain] and [no pain] condition categorized according to the preceding emotional

facial expression, i.e., happy, angry, painful, neutral, and no emotion in the **a** left dIPFC (dIPFC, MNI $-50, 2, 34$), **b** right mid-cingulate cortex (MNI $6, -4, 32$), and **c** LAI (MNI $-30, 26, 10$). All statistical parametric maps are thresholded at $p[\text{uncorr.}] < 0.001$ for $k > 10$. $*p < 0.05$; $**p < 0.01$. Error bar represents SEM

[angry+pain] versus [angry+no pain] ($t_{19} = 4.775$; $p < 0.001$) and between [neutral+pain] versus [neutral+no pain] ($t_{19} = 2.421$; $p = 0.026$) was observable. In addition, a significant differentiation between the conditions [happy+pain] versus [angry+pain] ($t_{19} = 3.281$; $p = 0.004$), [angry+pain] versus [neutral+pain] ($t_{19} = 2.910$; $p = 0.009$), and [happy+no pain] versus [neutral+no pain] ($t_{19} = 3.733$; $p = 0.001$) was detectable in the very same region.

As expected and consistent with the shown statistical parametric map for the contrast ‘positive effect of pain’, a significant differentiation between pain versus no pain collapsed over all emotions was observable in all three regions (left dIPFC/BA9: $t_{19} = 3.321$; $p = 0.004$; right mid-cingulate cortex: $t_{19} = 3.901$; $p = 0.001$; LAI: $t_{19} = 2.151$; $p = 0.045$) (Fig. 2).

Correlation results

Furthermore, we correlated the percent signal change derived from the above-outlined regions with psychological measures for each subject. We obtained one significant negative correlation between the scores of the subscale ‘difficulties identifying feelings’ of the Toronto Alexithymia Scale (TAS-20) and the signal change (in percent) for the condition [painful+pain] derived from the LAI ROI ($r_{\text{Pearson}} = -0.487$; $p = 0.04$; Fig. 3). All other correlations were non-significant.

Discussion

In the present study, we investigated the neuronal correlates of the pain-related empathic response and its modulation by

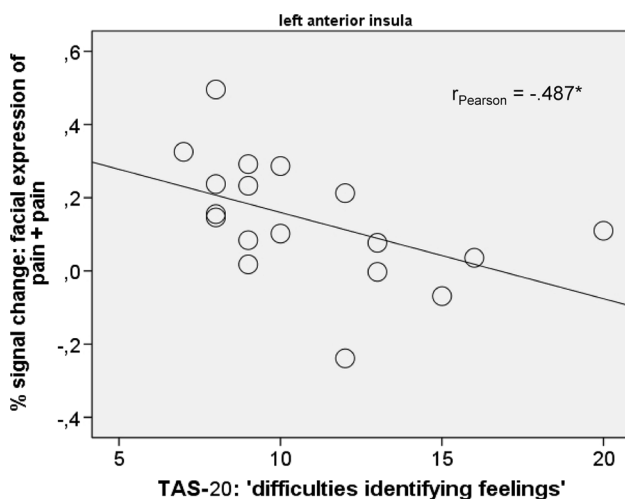


Fig. 3 Pearson correlations between fMRI signal change derived from the LAI activation for the condition [painful facial expression+pain] and the Toronto Alexithymia Scale (TAS-20), subscale ‘difficulties identifying feelings’

facial emotional expressions using functional magnetic resonance imaging in 20 healthy, male subjects. As expected and consistent with the existing literature (Lamm et al. 2011), the contrast ‘positive effect of pain’ revealed activations of brain regions commonly associated with empathy for pain and with the first-hand experience of pain, i.e., the left dIPFC, the right mid-cingulate cortex (mCC), and the LAI. In the left dIPFC, the (preceding) perception of an angry face caused an increased activation in the [pain] condition, whereas in the [no pain] no modulation by angry or painful facial expressions was observed. In the right mCC, a clear differentiation between [pain] and [no pain] independent of the shown emotion was detected. In the LAI, significant main effects for the factors ‘pain’ and ‘emotion’ were observed, whereas the interaction ‘pain × emotion’ did not yield a significant results.

Dorsolateral prefrontal cortex activation and emotion processing

Various studies using different imaging techniques have established the crucial role of the dIPFC in emotion processing, empathy in general and empathy for pain (Fan et al. 2011; Lamm et al. 2011; Ray and Zald 2012). In more detail, the lateral PFC is involved in emotion regulation, i.e., ‘changing the onset, duration, intensity, or content of an emotional response’ (Ray and Zald 2012), or—more specifically—cognitive reappraisal, i.e., the cognitive reinterpretation of (emotional) information for changing an emotional response (Ochsner and Gross 2005). More specifically, the dIPFC shows increased activation during distraction over an unregulated emotion (Ray and Zald 2012).

Regarding the present study, this could serve as an explanation for the increased activity during [angry+pain], since this condition is clearly associated with negative emotional valence or aversion. In a recent fMRI study in Chinese subjects, de Greck et al. (2012) reported an increased dIPFC activity related to empathy with anger in Chinese subjects compared to Germans. In addition, the enhanced dIPFC activity was associated with high subjective impression of empathy and could therefore reflect a protective mechanism from emotional hyperarousal (de Greck et al. 2012).

Mid-cingulate cortex, dIPFC, and anterior insula activation in empathy for pain

Various meta-analyses have found a consistent activation of the mid-cingulate cortex and the AI during empathy—irrespective of the induction method, i.e., cue-based versus picture-based, and the emotion empathized with (Fan et al. 2011; Lamm et al. 2011). As part of the ‘cortical mid-line structures’, the mCC plays a pivotal role in self-related processing, personal relevance (Enzi et al. 2009), and self–other distinction (for a review, see Northoff et al. 2006). Moreover, the cingulate cortex has extensive functional and anatomical connections to the AI, a brain region involved in interoceptive awareness (Critchley et al. 2004), emotion processing (Northoff et al. 2009), consciousness (Ullsperger et al. 2010), self-reflection (Enzi et al. 2009; Modinos et al. 2009), reward (de Greck et al. 2008), and empathy (Decety and Lamm 2006; Lamm et al. 2011). The AI receives afferents from the interoceptive (Craig 2009) and from the exteroceptive sensory system (Northoff and Panksepp 2008) and could be considered as crucial for linking interoception, exteroception, and emotion and, thus, for our ability to empathize. Since both brain areas—the mCC and the LAI—are active in empathy for pain and direct pain experience, these regions are at the centre of the above-described ‘shared representations’ approach (Heberlein and Atkinson 2009), i.e., the convergence of neuronal representations evoked by someone else being in an affective state versus one’s own experience of the same emotion (Walter 2012). In addition, both regions have been linked to the emotional–motivational component of pain (Walter 2012).

Lambie and Marcel (2002) suggested a three-level model of emotional experience that could probably serve as an explanation for the observed activation pattern in the insula. First, a neuropsychological arousal is linked to emotion processing that is associated with activity in limbic structures like the amygdala. The second-order experience of emotions encompasses the awareness of this arousal, i.e., interoception that is neurally implemented in the AI (Lambie and Marcel 2002; Silani et al. 2008). A reduced neuronal response in the AI is related to poor awareness of own and others’ feelings, a phenomenon commonly

called alexithymia (Ernst et al. 2013). This interpretation receives further support from the observed negative correlation between the TAS-20 subscale ‘difficulties identifying feelings’ and the LAI activity evoked by the condition [painful facial expression+pain], i.e., highly alexithymic subjects showed a reduced neuronal response in the LAI. In this context, it should be noted that alexithymic subjects showed less cerebral activation in the left dlPFC, the dorsal pons, and the left caudal ACC, accompanied by an attenuated activation of the right AI and the inferior frontal gyrus (Moriguchi et al. 2007). These alterations might reflect a basic disturbance related to emotional processing in alexithymia and underline the importance of the dlPFC as a regulating structure in empathy. As a limitation of this interpretation, it should be noted that using sophisticated techniques like multivoxel pattern analysis (MVPA) Corradi-Dell’Acqua et al. (2016) showed that only the right anterior insula shows a specific response patterns regarding affect and direct or empathic pain experience, whereas the LAI shows an unspecific response possibly associated with negative affect (see Zaki et al. 2016, for a recent discussion on this topic). In a recent fMRI study, Yoshino et al. (2010) investigated the neural response evoked by intraepidermal, painful stimulation in the context of emotional facial processing (sad, happy, and neutral). Using dynamic causal modelling (DCM) and psychophysiological interaction (PPI) analyses, the authors pointed out a modulation of amygdala to ACC activity by a sad emotional context and highlighted the impact of negative emotion processing on empathy for pain. Using short video clips of painful versus non-painful stimulation, Han et al. (2009) investigated the impact of neutral, happy, and painful facial expressions on pain processing. They reported a decrease in ACC activity if painful stimuli delivery to a neutral face was ‘intermixed with observation of painful or happy faces’. In addition, an enhanced activation of the bilateral (secondary) somatosensory cortex related to painful versus non-painful stimulation with regard to neutral facial expression (and compared to happy facial expressions) was observable (Han et al. 2009). They were not able to detect a significant effect of simultaneous painful facial expression on somatosensory cortex activity. The authors conclude that the somatosensory cortex forms an integrative structure incorporating the valence of (painful vs. non-painful) stimulation and facial emotions. Although using a different experimental design, the present study extends these findings by demonstrating that the dlPFC may contribute to this integrative process. Moreover, the authors reported a reduced empathic neural response associated with the *simultaneous* presentation of happy facial expression and painful situations. As an explanation, they propose two distinct mechanisms, either reduced attention with regard to the painful stimulus caused by conflicting facial emotional expressions

or a ‘deterioration of reality’ caused by this ambiguity (Han et al. 2009; Gu and Han 2007). In the present study, the reduced dlPFC/BA9 activity related to the condition [happy+pain], and thus conflicting stimuli, could therefore reflect the above-mentioned deterioration of reality. Or in other words, the observed activation for [angry+pain] in the very same region could be interpreted as ‘biological preparedness’ for painful stimuli caused by a negative emotional state. Furthermore, Han et al. (2009) investigated the connectivity pattern associated with valence, i.e., painful versus non-painful, and were not able to find ‘reliable stimulus changes in any brain areas [...] as a function of stimulus valence’ (Han et al. 2009). Of note and in addition to these results, we calculated a PPI model based on the dlPFC/BA9 seed. However, we were not able to detect a significant activation pattern reflecting effective connectivity related to stimulus valence that survives a reasonable statistical threshold, i.e., $p[\text{uncorrected}] < 0.001$.

Limitations

The study has five important limitations. (1) To avoid possible gender effects, only male subjects participated in this study. For this reason, we suggest to consider our results as preliminary. (2) Due to methodological reasons, subjects did not perform a trial-by-trial empathy rating. Nevertheless, all subjects reported at the end of each scanning session that they were able to empathize with the shown situation. (3) Although all subjects reported that they were able to distinguish the presented emotional facial expression, especially between angry and painful faces, only a poor neuronal differentiation was observable. (4) Regarding the correlation analysis, a correction for multiple comparisons was not performed since we followed an exploratory approach. The correlation analyses were limited to the LAI ROI and the TAS-20 subscales. Nevertheless, we consider these results as preliminary and suggest a replication in a different study population. (5) Regarding the regions-of-interest analyses, we consider the relatively small number of repetitions per condition (i.e. 12 repetitions) as a relevant shortcoming of the present study.

Conclusions

Taken together, our study suggests that the dlPFC has a modulatory impact on the processing of empathy-related stimuli. Moreover, limbic activation seems to correspond with alexithymia. Since the dlPFC is associated with cognitive reinterpretation of emotional information (with the objective of emotional distancing), this response pattern could therefore reflect a protective mechanism from emotional hyperarousal. Moreover, activation in the LAI showed a negative correlation with alexithymia,

emphasizing the integrating role of the AI between empathy, emotion and interoception. Future studies may expand on our findings by including clinical populations with difficulties in emotion processing, such as borderline personality disorder which is characterized by emotional dysregulation, affective instability, and alexithymic traits.

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