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Do words hurt? Brain activation during the processing of pain-related words

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ABSTRACT

Previous studies suggested that areas of the pain matrix of the human brain are recruited by the processing of pain-related environmental cues such as pain-related pictures or descriptors of pain. However, it is still sketchy whether those activations are specific to the pain-relevance of the stimuli or simply reflect a general effect of negative valence or increased arousal. The present study investigates the neural mechanisms underlying the processing of pain-related, negative, positive, and neutral words. Pain-related words were matched to negative words regarding valence and arousal, and to positive words regarding arousal. Sixteen healthy subjects were scanned during two tasks, imagination and distraction, using functional MRI. When subjects were instructed to image a situation associated with the word presented (imagination task), we found increased activation within dorsolateral prefrontal cortex (DLPFC), inferior patietal gyri (IPG), and precuneus when processing pain-related words compared to other words. However, when attention was focused on a foreground task and words were presented in the background (distraction task), we found a decrease in activation within dorsal anterior cingulum (dACC) and a relative increase in activation within the subgenual ventral anterior cingulum (sACC) when processing pain related words compared to other words. Thus, activations to pain-related words are strongly modulated by the attention demands of the task. Most remarkably, the differences in processing pain-related words compared to non-pain-related words are specific to the pain-relevance of the words and cannot simply be explained by their valence or arousal.

1. Introduction

Psychological variables such as attentional and emotional states, hypnotic suggestion, and expectation are recognised as modulators of the perception and the processing of noxious events in humans [8,16,18,21–23,28,31,45]. It is also known that environmental pain-related visual and semantic cues can activate the pain matrix or, at least, parts of it even when no noxious stimulus is applied [2,20]. More specifically, viewing facial expressions of pain was found to activate medial prefrontal cortex (PFC), perigenual anterior cingulate cortex (ACC), primary and secondary somatosensory cortices (S1 and S2, respectively), and insular cortex (IC) during the presentation of male pain faces as compared to male anger faces [36]. Additionally, enhanced activation within pain-related regions was demonstrated in individuals anticipating, but not receiving a noxious stimulus [34,39], during hypnotically induced pain [5], imaging pain in others, and self-referred pain imagination [15,37]. Only a few studies investigated the effect of verbal pain descriptors on neural responses. Semantic pain-related priming during painful laser stimulation was investigated by our group [6,44]. We found larger positive amplitudes in laser-evoked potentials when migraine patients and healthy controls were primed with pain-related words compared to neutral words. Enhanced positive event-related potentials to pain-related words per se, especially to affective pain-related words, were found in two EEG studies with chronic pain patients and patients suffering from depression, respectively [24,38]. To our knowledge, there are three fMRI studies on the processing of pain-related word stimuli so far. Gu and Han reported enhanced activation within middle PFC and S2 during a rating task in contrast to a counting task [11]. The retrieval of pain-related memories in response to pain-related words produced increased activation within left caudal ACC and inferior frontal cortex compared to that of non-painful memories in response to non-pain-related words [17]. Similarly, Osaka et al. found a stronger activation within dorsal ACC during listening to expressions highly suggestive of pain compared to nonsense verbal expressions [26].

Based on the concept of neural memory networks and correlation learning [14,30], we suggested that processing of pain-associated verbal cues activates not only neural structures associated with language but also structures of the pain matrix. However, previous studies solely explored the effect of pain versus neutral or

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positive conditions. Thus, our first aim was to investigate whether the bias towards pain-related words is related to pain itself or to the negative valence of such stimuli. Furthermore, it has been shown that implicit processing of pain-relevant information affects reaction time and activates the pain matrix [1,36], but sufficient imaging data are lacking. Therefore, our second aim was to find out whether the neural effects of pain-related words depend on the attention focus during the activation tasks. To address those aims the neural effects of pain-related words compared to those of neutral, positive affective, and negative affective words were measured during two tasks (imagination and distraction) with functional MRI.

2. Subjects and methods

2.1. Subjects

Sixteen right-handed healthy volunteers (8 males and 8 females, 22.8 ± 2.8 years old) participated in the experiment. All subjects were native German speakers. They provided informed consent to participate in the study. Right-handedness was assessed using the Edinburgh Handedness Inventory [25]. Subjects reported no history of chronic pain diseases and were free of medication.

2.2. Stimuli selection

A primary sample of 36 pain-related word stimuli was collected from pain questionnaires (e.g. McGill Pain Questionnaire) and was completed by clinical personnel. Words of the other categories were adopted from the material of previous studies on emotional word perception of our group. Prior to the fMRI experiment, an independent sample of 28 subjects rated a total number of 156 German adjectives regarding valence, arousal, and pain-relatedness. Numeric rating scales were used to assess valence (0 = most negative, 10 = most positive), arousal (0 = not aroused, 10 = very aroused), and pain-relevance (0 = not pain-related, 5 = strongly pain-related) of the words. Words producing significant differences between male and female participants on the three scales were excluded. Based on these data, we selected a final sample of 10 words for each group, i.e. pain-related words and neutral, negative affective, and positive affective words (see Table 1). Care was taken that neutral, negative affective, and positive affective words were not used as common descriptors of pain in German language. Words were matched according to length and word frequency in everyday German language (using Cosmas Version 3.6.1., www.ids-mannheim.de/cosmas2). As expected, words differed in terms of their pain-relevance. Pain-relevance ratings were 0.15 ± 0.16 for the positive affective, 0.31 ± 0.17 for neutral, 1.05 ± 0.25 for negative affective and 3.14 ± 0.38 for pain-related words, respectively. Valence ratings of pain-related and negative words did not differ significantly, and there was no significant difference in arousal ratings of pain-related, negative, and positive affective words.

2.3. Tasks and study design

The experimental paradigm included two covert activation tasks performed during two separate counterbalanced scanning runs: imagination (run 1) and distraction (run 2). Each run consisted of 16 stimulus sequences. Within each sequence, a block of five adjectives of one descriptor category was presented in pseudo-randomized order with a presentation time of 4.1 s per word and an inter stimulus interval between succeeding words of 0.1 s. Each block lasted for 21 s (7 fMRI volumes) and was followed by a delay period (duration = 11 s), a motor response (decision task, duration = 7 s), and the baseline condition (fixation cross, duration = 13 s) (see Fig. 1). During run 1, participants were instructed to silently read each word presented at the video screen and to imagine a situation or a sensation associated with the word. After each block they were asked to decide whether the previously presented adjective belonged to one of two descriptor categories (e.g. "A = pain" or "B = neutral") by pressing a button with the right hand. During run 2, subjects were instructed to silently count the vowels of the words within each block. After each block, they were instructed to choose the correct number of vowels out of two total numbers presented (e.g. "A = 12" or "B = 15").

2.4. Behavioral assessment

A numeric 0–10 rating scale was used to assess the difficulty of the two tasks (0 = very easy and 10 = very difficult). A comparison of the imagination and the distraction condition regarding difficulty was made using t-tests. Psychopathology as a potential confounding factor was assessed using German versions of the Symptom Check List (SCL-90-R) [9] and the Beck Depression Inventory (BDI-2) [13]. To estimate subjects' pain experiences, we used numeric 0–10 rating scales to assess the intensity of the last pain event remembered (0 = no pain, 10 = maximum pain intensity), pain-associated impairment during the last 6 months, and during lifetime (0 = no impairment, 10 = maximum impairment). We also asked for the date, duration, and nature of the last pain event and for the last pain medication taken.

2.5. fMRI-data acquisition and analysis

In a 3-Tesla magnetic resonance scanner (Magnetom Vision plus, Siemens, Medical Systems, Erlangen, Germany), two runs of 305 volumes were measured using a $T2^*$ weighted echo-planar sequence (time to echo [TE] = 30 ms, flip angle = 90°, matrix = 64 × 64, field of view [FOV] = 192 mm, scan repeat time [TR] = 2.8 ms). Each volume comprised 40 axial slices (thickness = 3 mm, no gap, in-plane resolution = 3 × 3 mm) parallel to the intercommissural plane (AC–PC-plane). Additionally, a high-resolution T1-weighted anatomical volume was recorded (192 slices, TE = 5 ms, matrix = 256 × 256 mm, resolution = 1 × 1 × 1 mm).

Table 1
Word stimuli.

Pain	Negative	Neutral	Positive
Quälend (excruciating)	Eklig (disgusting)	Gehend (pacing)	Streichelnd (stroking)
Lähmend (paralysing)	Feindlich (adversarial)	Eckig (angled)	Wärmend (warming)
Zermürbend (grueling)	Intrigant (scheming)	Kurzhaarig (short-haired)	Erquickend (refreshing)
Peinigend (tantalising)	Widerlich (abhorrend)	Eiförmig (ovaliform)	Beschwingend (elating)
Plagend (afflicting)	Warzig (warty)	Gewölbt (arched)	Himmlisch (celestial)
Kneifend (nipping)	Schimmlig (mouldy)	Aschblond (ash-blond)	Flirtend (flirting)
Quetschend (sqeezing)	Stinkend (smelling)	Klappbar (hinged)	Kuschelnd (cuddling)
Bohrend (drilling)	Verdreckt (dirty)	Kubisch (cubic)	Küssend (kissing)
Kolikartig (colicky)	Angsteinflößend (scary)	Traubenförmig (aciniform)	Hocherotisch (highly erotic)
Krampfartig (crampy)	Hasserfüllt (hate-filled)	Auditiv (auditory)	Bezaubernd (bewitching)

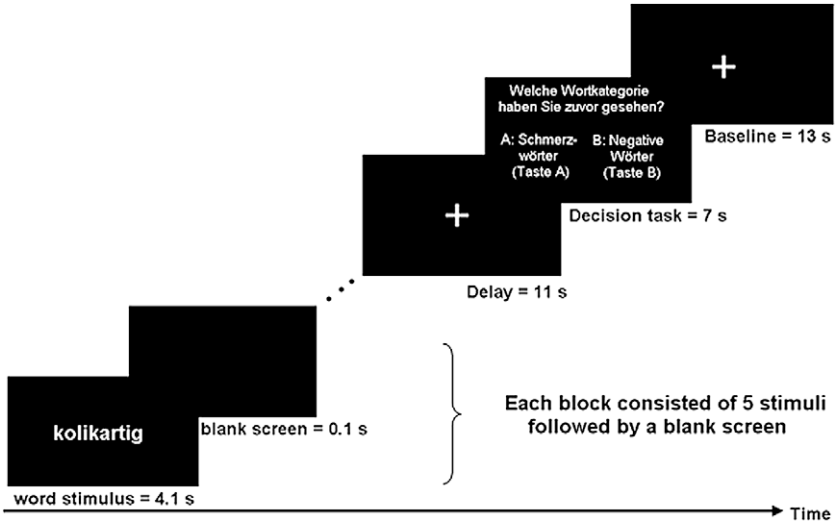

Fig. 1. Stimulus protocol.

Imaging data were pre-processed and analysed using Brain Voyager QX, Version 1.10 (Brain Innovation, Maastricht, The Netherlands). The volumes were realigned to the first volume in order to minimize the effects of head movements on data analysis. Further data pre-processing comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) as well as temporal smoothing (high pass filter: 3 cycles per run). Anatomical and functional images were co-registered and normalized to the Talairach space [40].

Statistical analysis of fMRI-data was performed by multiple linear regression of the signal time course at each voxel. The expected blood oxygen level-dependent (BOLD) signal change for each event type (predictor) was modelled by a canonical hemodynamic response function (modified gamma function). Voxelwise analyses were inspected within the whole brain. To strike a balance between type I and type II errors, we tested whether the detected clusters survived a correction for multiple comparisons. We used the approach as implemented in Brain Voyager which is based on a 3D extension of the randomization procedure described by Forman et al. (1995) [7,10]. First, voxel-level threshold was set at $p < 0.005$ (uncorrected). Threshold maps were then submitted to a correction for multiple comparisons for each contrast. The correction criterion was based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold yielding a cluster-level false-positive rate of 5% was applied to the statistical maps of each contrast [39]. All clusters reported in this article survived this ROI-based control of multiple comparisons.

Main effect analyses were performed for the two conditions separately. Random effect group analyses were performed for each relevant contrast: (1) pain-related words – neutral words (imagination), (2) pain – negative (imagination), (3) pain – positive (imagination), (4) pain – neutral (distraction), (5) pain – negative (distraction), (6) pain – positive (distraction), and (7) pain (imagination) – pain (distraction).

3. Results

3.1. Behavioural data

Two tasks were solved by the subjects, imagination of a situation or a sensation associated with the word (imagination task), and counting the vowels of the word sequence (distraction task). Ratings on task difficulty were significantly higher for the imagination (mean = 2.38 ± 1.46) as compared to the distraction task (mean = 1.38 ± 1.36, $T = 2.93$, $p < .05$). Low mean ratings indicate that both tasks were easy to solve and did not demand strong cognitive effort. The mean of SCL-90-R score was 21.19 ± 20.84 and the mean BDI-2 score was 3.94 ± 3.59 for the whole group. There were two subjects with slightly increased scores indicating a minimal depression (minimal depression relates to scores between 9 and 13) [13]. This indicates that our subjects were free of clinical meaningful psychopathological symptoms. Subjects reported that pain-related impairment during the last 6 months was 1.93 ± 2.12 and the average pain-related impairment for the whole life span was indicated as 0.87 ± 1.13. We conclude that subjects were not notably impaired by pain during the last 6 months and during lifetime. The last painful event was at least 1 week ago (intensity rated as 3.86 ± 1.92 on a 0–10 scale). Subjects did not experience present pain at the beginning of the experiment and were not under pain medication.

3.2. fMRI data

3.2.1. Processing of pain-related words

When comparing the processing of pain-related words with the baseline condition during the imagination task, we found activation within dorsal ACC (dACC), left anterior IC, bilateral inferior frontal gyrus, dorsolateral prefrontal cortex (DLPFC), primary somatosensory cortex (S1), left superior parietal gyrus and precuneus, the left superior and middle temporal gyri, bilateral middle and inferior occipital gyri, bilateral thalamus, and within left caudate body. During the distraction task, we found activation within ventral ACC (vACC) and dACC, bilateral medial frontal gyrus, anterior IC, inferior frontal gyrus, DLPFC, S1, posterior cingulate cortex (PCC), bilateral middle and inferior occipital gyri, left and right thalami, and within left caudate body during the processing of pain-related words (see Table 2).

Direct comparison between imagination and distraction revealed increased activation within left superior and inferior frontal gyri, left IC, left middle and inferior temporal gyri and left precuneus (BA 39) and decreased activation within right precuneus (BA 7) and middle occipital gyrus during the imagination condition.

Table 2
Brain activation during imagination and distraction against baseline (deactivated clusters are not reported).

Region right/left		Imagination			*t*	Distraction			*t*
		x	*y*	*z*		*x*	*y*	*z*	
Ventral ACC	R					18	41	−3	4.87
Dorsal ACC	R/L	−8	8	47	5.36	−9	5	46	6.36
Anterior insula	L	−46	14	5	9.24	−27	17	16	6.40
	R					33	17	10	6.40
Inferior frontal gyrus	L	−45	41	13	12.18	−36	1	34	7.42
	R	36	21	9	5.58	55	−1	43	4.84
Medial frontal gyrus	R/L					−6	−4	55	8.34
DLPFC	L	−42	17	34	12.65	−39	2	31	7.23
	R	45	23	34	4.58	48	26	40	4.20
Postcentral gyrus	L	−45	14	31	12.99	−54	−10	46	5.93
	R	33	17	22	6.28	45	−34	52	4.07
Posterior cingulate cortex	L					−24	−70	31	8.23
	R					12	−73	40	8.16
Superior parietal gyrus/precuneus	L	−45	−40	43	6.43				
Superior and middle temporal gyri	L	−51	−19	−2	7.01				
Middle and inferior occipital gyri	L	−24	−79	−14	21.83	−24	−88	−14	13.62
	R	21	−91	−5	11.48	21	−91	−5	10.64
Thalamus	L	−9	−13	13	5.52	−24	−22	1	4.42
	R	21	−19	16	5.22	24	−31	10	3.79
Caudate body	L	−18	5	4	5.62	−21	2	19	6.21

Coordinates refer to the most significant voxel within each cluster, *t* = t-value of the most significant voxel; R = right hemisphere; L = left hemisphere; R/L = right and left hemispheres; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex.

3.2.2. Contrasts of brain activation during imagination while processing different word categories

Contrasts between word categories showed stronger activation within left inferior parietal gyrus (IPG), precuneus, and within left DLPFC when pain-related words were processed as compared to all other conditions (see Fig. 2 for comparison of pain-related words with negative words). Specifically, when comparing pain-related words and negative words, right IPG and precuneus exhibited stronger activation during the processing of pain-related words, while the medial frontal gyrus, left inferior temporal gyrus, and left caudate body exhibited more activation during the processing of negative but non-pain-related words. Compared to positive words, bilateral DLPFC, IPG, posterior cingulum, left inferior and middle temporal gyri, and precuneus showed increased activation whereas ACC, left postcentral gyrus and medial frontal gyrus showed decresed activation during the processing of pain-related words. Compared to neutral words, left DLPFC, IPG, bilateral precuneus, medial/superior frontal gyrus, and posterior cingulum showed increased activation whereas ACC, right postcentral gyrus, posterior insula/operculum, bilateral inferior temporal gyri, and

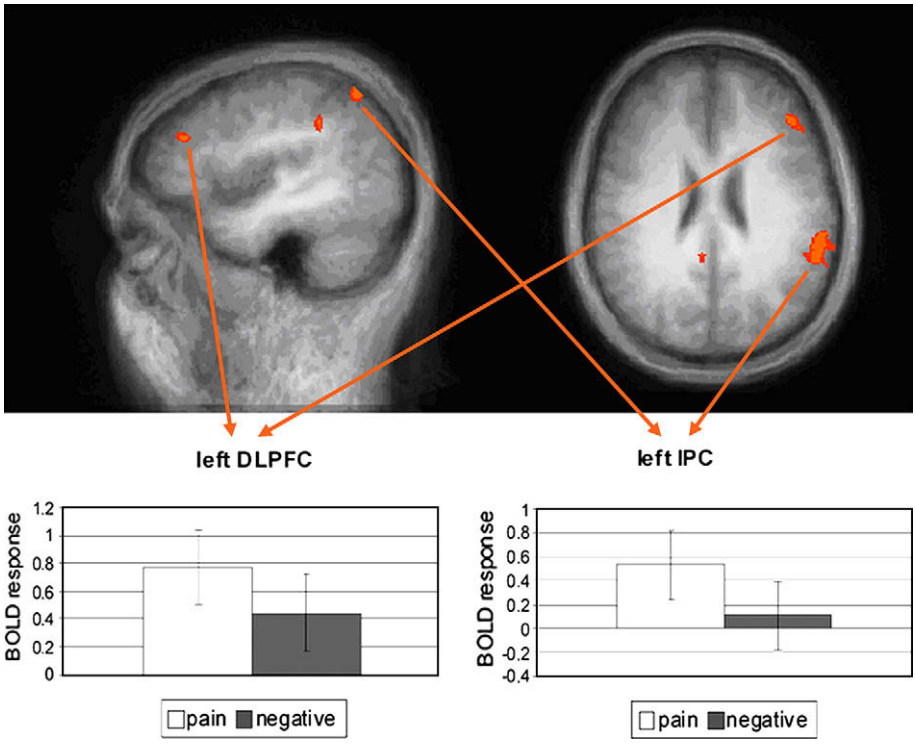

Fig. 2. Sagittal and transversal views of the contrast pain-related words against negative affective words during explicit processing (EXP) within left DLPFC and IPG at $x = -42$, $y = 33$, $z = 25$. The plot below shows mean BOLD response for activated clusters.

Table 3
Contrasts between pain-related words and other word categories during imagination ($p = 0.05$, corrected).

Region right/left		Pain – Neutral				Voxel	Pain – Negative				Voxel	Pain – Positive				Voxel
		x	*y*	*z*	*t*		*x*	*y*	*z*	*t*		*x*	*y*	*z*	*t*	
Ventral/dorsal ACC	R/L	−3	35	4	−5.08	493	18	5	31	−6.92	4044	−6	38	7	−11.66	7765
Postcentral gyrus	L											−36	−22	34	−4.28	239
	R	57	−25	40	−5.54	2554										
Posterior insula/operculum	R	39	−4	10	−5.11	950										
DLPFC	L	−36	44	28	4.97	339	−42	33	25	4.52	432	−42	30	31	5.62	3540
	R											45	26	37	5.18	820
Inferior parietal gyrus	L	−60	−37	25	4.44	203	−54	−40	28	5.01	1814	−36	−49	34	5.57	2322
	R						42	−49	46	5.05	602	45	−43	40	4.57	1440
Posterior cingulate cortex	R/L	−3	−22	25	5.08	976						0	−34	19	4.69	427
Precuneus	L	−12	−67	31	4.27	225	−12	−70	37	4.44	315	−12	−74	55	4.87	497
	R	6	−64	31	5.10	566	9	−67	31	4.88	504					
Medial frontal	R/L	0	59	16	−5.30	263	0	5	46	−6.64	1507	0	59	19	−8.96	4417
Medial/superior frontal	R/L	3	38	49	4.57	397										
Inferior temporal gyrus	L	−45	−52	−11	−6.25	1053	−63	−10	−17	−6.63	949	−48	−61	−11	5.34	1288
	R	51	−43	−8	−5.57	3107										
Middle temporal gyrus	L											−63	−7	−14	6.44	784
Parahippocampal gyrus	R	27	−25	−14	−5.61	1191										

Coordinates refer to the most significant voxel within each cluster, *t* = *t*-value of the most significant voxel; voxel = number of voxels within the referred activated cluster; R = right hemisphere; L = left hemisphere; R/L = right and left hemispheres; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex.

right parahippocampal gyrus, and medial frontal gyrus showed decreased activation during the processing of pain-related words (see Table 3).

3.2.3. Contrasts of brain activation during distraction while processing different word categories

We found activation within the subgenual part of ventral ACC (sACC) and deactivation within dACC during the processing of pain-related words as compared to processing of all other word categories (see Fig. 3 for comparison of pain-related words with negative words). Comparing the processing of pain-related and negative words, deactivations were exhibited within bilateral anterior IC, left posterior IC and operculum (S2), medial frontal gyrus, and superior frontal gyrus. Compared to positive words, subjects exhibited reduced activation within medial frontal and right superior temporal gyri when processing pain-related words (see Table 4).

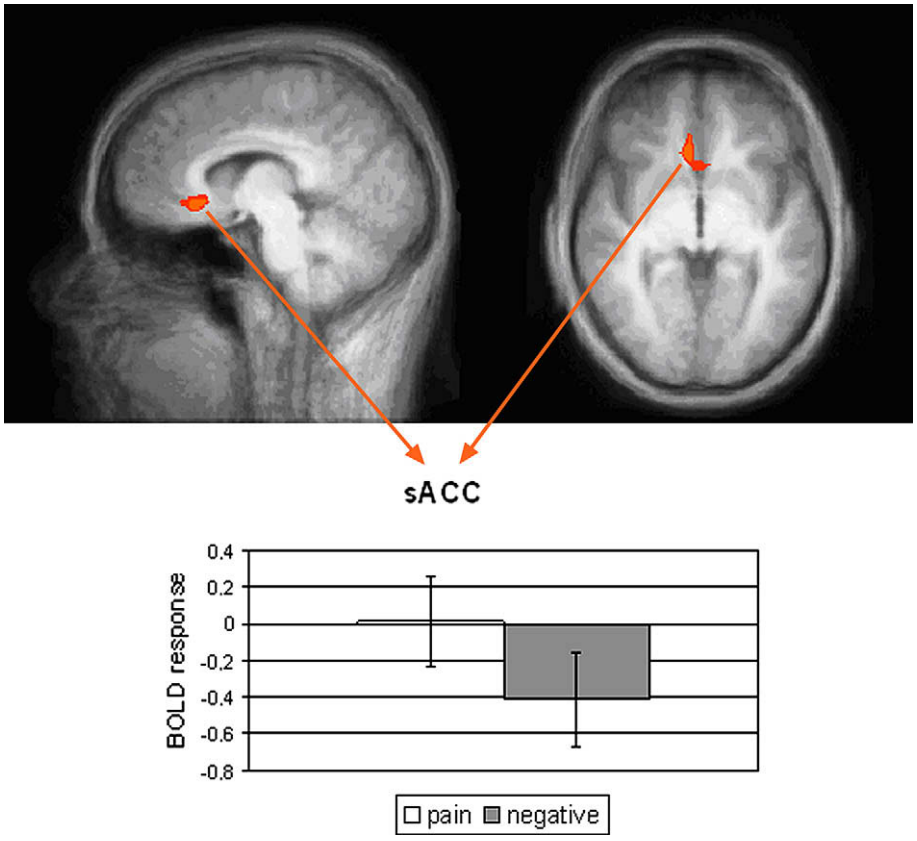

Fig. 3. Sagittal and transversal views of the contrast pain-related words against negative affective words during implicit processing (IMP) within sACC at $x = 7$, $y = 24$, $z = -2$. The plot below shows mean BOLD response for activated clusters.

Table 4
Contrasts between pain-related words and other word categories during distraction ($p = 0.05$, corrected).

Region right/left		Pain – Neutral				Voxel	Pain – Negative				Voxel	Pain – Positive				Voxel
		x	*y*	*z*	*t*		*x*	*y*	*z*	*t*		*x*	*y*	*z*	*t*	
Ventral ACC (subgenual)	R	6	17	1	5.74	482	9	23	−5	5.26	1083	3	14	−8	4.98	217
Dorsal ACC	R/L	6	38	22	−5.31	527	0	32	13	−5.17	5215	9	38	28	−4.38	335
Anterior insula	L	−33	23	1	−5.67	324	−30	23	1	−5.78	2294					
	R						26	17	−2	−4.07	386					
Posterior insula/operculum	L	−39	−7	−2	−4.13	196	−33	−13	1	−4.20	309					
	R	42	−31	22	−5.29	399										
Superior frontal gyrus	R	12	59	40	−5.29	788	21	56	34	−4.95	1130					
Medial frontal	R/L						6	1	46	−5.18	614	−3	50	28	−4.16	211
Superior temporal gyrus	R											42	−37	19	−5.76	298
Middle temporal gyrus	R	48	−34	1	−6.41	309										
Fusiform gyrus	L	−51	−46	−20	−4.73	850										

Coordinates refer to the most significant voxel within each cluster, *t* = *t*-value of the most significant voxel; voxel = number of voxels within the referred activated cluster; R = right hemisphere; L = left hemisphere; R/L = right and left hemispheres; ACC = anterior cingulate cortex.

4. Discussion

The aim of the present study was to investigate brain activation elicited by pain-related compared to negative, positive, and neutral words during two attention tasks. Our results indicate that pain-related words activate regions associated with the pain matrix, especially when subjects were explicitly attending to words. These activations differ significantly from activations induced during the processing of non-pain-related words within regions associated with the cognitive dimension of pain such as DLPFC and parietal cortex.

4.1. Processing of pain-related words

The presentation of pain-related stimuli activated regions known from studies on single word reading such as inferior frontal gyrus and superior temporal gyrus [29,32] as well as regions of the pain matrix such as dACC, DLPFC, anterior IC, postcentral gyrus (S1), IPG, and thalamus [2,28,41] during both the imagination and the distraction condition. Our findings correspond to prior studies on the processing of pain-relevant cues that found activation within left inferior frontal gyrus [17], ACC [37], anterior IC [11], posterior parietal cortex [26], S1, and prefrontal regions [36].

Activated clusters were found within superior parietal gyrus, precuneus, and superior/middle temporal gyri during the imagination but not during the distraction task. The engagement of the temporoparietal system (mainly left-hemispheric) may be due to the specificity of these regions to word comprehension and reading and to directed attention towards the stimulus [12,35]. During the distraction but not during the imagination task, activated clusters within vACC, right anterior IC, medial frontal cortex, and bilateral posterior cingulum were found. These regions are related to the processing of conflict during distraction tasks [33]. Additionally, activation within midcingulate cortex was found in studies on sustained attention using Stroop tasks [27]. Stroop-task induced distraction during painful stimulation leads to increased activation within orbitofrontal cortex and perigenual ACC (pACC) [3,42]. Therefore, the additional activations we found during the distraction condition might be due to the attention demands of the task, i.e., solving the counting task without focusing on the meaning of the pain-related word. Comprehensively, activations we found during the processing of pain-related words include structures of the pain network, the reading network (especially during explicit stimulus perception) and the network of conflict processing (especially during distracted attention).

4.2. Processing of pain- vs. non-pain-related words during imagination

The main finding during explicit processing of pain-related words (imagination) is the stronger recruitment of DLPFC, IPG, and precuneus as compared to that during the processing of other word categories. The differences are mainly located within the left hemisphere, probably traced back to the fact that subjects were exposed to a language task. The above-mentioned regions are known to mediate the cognitive dimension of pain, more precisely, the perception, localisation and encoding of the attended pain-related stimulus [27]. Therefore, we assume that pain descriptors generate a pain-specific bias within the attention system towards such information. This may explain previous findings on the behavioural and brain electrical priming effect of pain-related words [6,44]. Recruitment of the medial prefrontal cortex has previously been shown by rating the pain-intensity of painful actions as compared to counting letters [11]. This finding might also be interpreted as a sign of pain-specific allocation of attention resources. Osaka et al. found activation within ventrolateral prefrontal cortex during listening to onomatopoeia words expressing affective pain as compared to the listening of nonsense words, and interpreted their results in terms of attention-driven semantic retrieval and generating imaginary pain [26]. We instructed subjects to imagine the sensation connoted by the words presented. Thus, the connotation of pain-related words seems to produce a more conspicuous effect within attention-related regions as compared to the connotation of non-pain-related words. Notably, this effect seems to be due to the pain-relevance and not due to a general arousal or valence effect of words as previously shown by Kensinger and Schacter [19].

4.3. Processing of pain- vs. non-pain-related words during distraction

During the distraction condition, we found a relative increase in the activation of the subgenual division of perigenual ACC (sACC) for pain-related words. More precisely, when comparing BOLD changes taking into account baseline levels, we found a greater deactivation during the processing of neutral, negative, and positive words as compared to the processing of pain-related words. According to Vogt et al., sACC is involved in conditioned and autonomic responses as well as in the expression of emotional states [43]. Peyron et al. suggested that activation within pACC is not generally related to emotional processing of pain, but rather to the anxiety and stress caused by painful events [27]. Transferred to our results, subjects might have experienced a relative decrease in stress level during processing of pain-unrelated words but not during processing of pain-related words as compared to baseline

activation. But taking into account that our stimuli were matched according to arousal, it seems unlikely that differences in activation are due to the intensity of the stress responses.

An alternative explanation for the relative activation in sACC might be that counting vowels represents a more competing task to the perception of pain-related words as compared to that of other word categories. The cognitive subdivision of the ACC (dACC) modulates attention and executive functions and monitors competition during task performance. The affective subdivision (vACC/pACC) is involved in assessing salience of emotional information [4]. Hence, we consider that pain-related words might have a specific survival value and induce greater emotional interference, resulting in a relative increase in pACC and a decrease in dACC activation. Simon et al. found activation within pACC when contrasting the brain activation during the processing of pain faces and anger faces [36]. Enhanced activation was interpreted as a substrate of inhibiting task-irrelevant pain-related information during implicit task performance. Bantick et al. reported that enhanced activation within pACC and decreased activation within other pain-related regions, e.g. the midcingulate cortex, occur during pain and cognitively demanding Stroop interference [3]. They suggested that activation of pACC is linked to the relative deactivation within other pain-related areas via reciprocal inhibition. We also found deactivation within dACC (close to midcingulum) during the processing of pain-related words as compared to the processing of the other words. Therefore, the relative activation of sACC and deactivation of dACC during the processing of pain-related words might reflect the inhibition of salient pain-relevant information during performing a distraction task.

5. Conclusion

Our study provides evidence that the processing of pain-related words leads to activations within regions of the pain matrix. We show for the first time that the processing of explicitly presented, pain-related verbal stimuli does not merely reflect a non-specific response induced by the affective quality of stimuli, but includes specificity of pain-relevance. Secondly, we found that the regions activated by pain-related words differ according to the attentional focus induced by the tasks. During the imagination task, the specificity of pain-related words is reflected in a central nervous activation of regions associated with the cognitive dimension of pain such as the DLPFC and the IPG. Concerning the distraction task, we suggest that relative sACC activation and dACC deactivation are associated with the concurring nature of pain-relevant semantic information during solving a foreground task.

Our findings underline that the perception of pain-related words changes the central nervous processing associated with the cognitive dimension of pain. On a broader view, these changes may alter the processing of acute and chronic pain sensations through associative learning as the basis for verbal priming effects within the pain-associated neural network. In this context, the investigation of the processing of pain-related words in chronic pain sufferers might be of great interest. Furthermore, the potential priming effects of those verbal descriptors by modifying the cognitive dimension of the pain matrix should be taken into account in studies with healthy and chronic pain subjects.

Conflict of Interest

The authors of this manuscript have no financial or other relationship that might lead to a conflict of interest.

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