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Retrieving Autobiographical Memories of Painful Events Activates the Anterior Cingulate Cortex and Inferior Frontal Gyrus

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Abstract: **Patients will often reflect on the meaning of a painful episode, as, for example, when completing questionnaire measures of subjective pain experience or in clinical interviews. Neuroimaging studies of the human cortical and subcortical physical pain response have identified a neural network consistently referred to as the "pain matrix." We used functional magnetic resonance imaging to investigate whether the pain matrix could be activated through the retrieval of memories relating to previously painful events, in the absence of any direct peripheral noxious input. Fourteen pain-free participants were explicitly instructed to recall autobiographical memories of painful episodes in response to pain-related words and non-painful episodes in response to equally salient but non-pain words. Memories triggered by pain-related words produced significantly greater activation of left caudal anterior cingulate cortex (BA32′), and left inferior frontal gyrus (BA44, extending to BA47/45) more than memories triggered by equally salient but non-pain words. We suggest that these activations demonstrate a semantic retrieval process for pain-related memories, which may provide a means of cognitively reappraising the memory of the painful episode, thus allowing the person to elaborate on the circumstances surrounding the event, without physically re-experiencing it.**

Perspective: ***The present study reveals a putative neural mechanism for the retrieval of autobiographical memories of previously painful events, which may provide a means of cognitively reappraising a painful episode, without physically re-experiencing it. This finding has implications for understanding disease mechanisms of chronic pain and their impact on subsequent treatment.***

Key words: *Functional magnetic resonance imaging, memory, pain, words, semantic.*

Neuroimaging techniques of positron emission tomography and functional magnetic resonance imaging (fMRI) have identified a brain nociceptive system consistently activated in response to physically noxious stimuli, which has been referred to by several authors as the "pain matrix."[1,3] Melzack and Katz[24] postulated a three-dimensional pain experience including sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. The findings of neuroimaging studies have correlated the structures of the pain matrix to each dimension. For example, the sensory-discriminative pain dimension has been empirically linked to primary (SI) and secondary (SII) somatosensory cortices, thalamus, and insular cortex.[2] The affective-motivational pain dimension is associated with activation of insular cortex and rostral-ventral anterior cingulate cortex (ACC; BA32/BA24),[37] whereas the parietal and prefrontal cortices and caudal ACC (BA32′/BA24′)[36] are linked to the cognitive-evaluative pain dimension.[8] The effect that recalling previous painful events has on the pain matrix has not yet been investigated.

Behavioral studies have provided evidence for the differential processing of affective, cognitive, and sensory aspects of pain. For example, memory biases for pain-related words have been demonstrated in chronic pain

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populations[10,39] and pain-free individuals.[19] Such memories can be subdivided into (i) somatosensory memory, which allows for the re-experiencing of the pain, and (ii) cognitive pain memory, which can include pain experience memory, that is, remembering the sensory, intensity, and affective qualities of pain without re-experiencing it, and pain event memory, that is, remembering the circumstances in which the pain was experienced.[25]

The current study used autobiographical memories to investigate if recalling a painful event activates the pain matrix. Autobiographical memory is unique in allowing conscious recollection of the event and the context in which it occurred. Previous studies of autobiographical memory have successfully used words as cues for memory retrieval.[14,15,22] When examining the pain experience, words have been shown to have significant advantages over pictorial depictions of painful events.[4,23] Recently, Hauk et al[16] demonstrated that word stimuli can activate brain regions linked to the semantic nature of the stimuli. In an event-related fMRI study, a passive reading task containing action words relating to arm and leg movements was found to activate areas of the motor and premotor cortex in a somatotopic manner. A third condition, containing less semantically and physically related words, did not demonstrate somatotopic activation. The authors interpreted their findings within an associative model of word processing whereby neural assemblies, which are located in brain areas related to word perceptions, process the meaning of word stimuli. These findings indicate that motor and sensory components of actions, which are semantically derived, can activate regions of the brain involved in the original act. The implications of this for pain processing are that acts that result in a painful event are stored in memory and can be retrieved when that event is recalled through reading a word cue. Indeed, the usefulness of psychometric measures of clinical pain experience, derived from questionnaires, relies on this very mechanism.

In the present study, we hypothesized that the recollection of past pain episodes, triggered by pain-related words (compared with activations triggered by non-pain words), would preferentially activate the cognitive and affective regions of the pain matrix, specifically prefrontal and insula cortices, and both rostral-ventral and caudal ACC. The cue words were not physically localized to a specific body part, and, as such, activation of SI, SII, and thalamus was not predicted. If proven, these data will be the first to demonstrate that the retrieval of autobiographical memories allows for the cognitive reappraisal of both the sensory qualities of a painful event and the circumstances in which it occurred, through activation of the pain matrix.

Materials and Methods

Fourteen healthy, pain-free participants (5 men, 9 women), aged between 20 and 32 years (with a mean age of 23.7 years), gave fully informed written consent of their willingness to participate in this study, which had Sefton Research Ethics Committee approval. Participants were predominantly right-handed (10/14) as assessed by the Edinburgh Handedness Inventory[26] and were free from neurological or systemic disease.

Table 1. Complete List of Pain-Related and Non-Pain Word Stimuli Used in the Study

Pain Words		*Neutral Words*	
Bruise	Itch	Decorate	Banister
Hurt	Hurting	Wallpaper	Tidy
Discomfort	Irritation	Bookcase	Homely
Swollen	Sore	Fridge	Radiator
Suffering	Smarting	Thatched	Hob
Cramp	Nipping	Footstool	Loft
Twinge	Injury	Hoovering	Stool
Agony	Numb	Wardrobe	Attic
Blister	Sprain	Plumbing	Shelf
Rasping	Ache	Spacious	Sofa
Scald	Gash	Roofing	Ironing
Stinging	Pinch	Pillow	Patio

The task stimuli consisted of 24 pain-related (P) and 24 non-pain (N) words. Pain words were generated from a list derived from several sources (including the McGill Pain Questionnaire) with ambiguous items removed. For the non-pain words, several familiar household items were chosen (for a full list of the words used, see Table 1). Task stimuli were controlled for frequency, length, and number of syllables[18] and did not differ significantly in terms of noun imageability [$F = 2.362$, $P = .160$, NS, as assessed by the University of Western Australia Psycholinguistic Database; www.psy.uwa.edu.au/MRCDatabase]. Words were visually presented to participants while in the scanner by back-projection onto a screen visible through a mirror in the head coil, using an LCD projector (Epson LMP7300: Seiko Epson Corporation, Nagano, Japan) connected to a Toshiba Laptop computer (Toshiba America, Inc., New York, NY), covering 9° × 6° of visual angle.

Using a boxcar design, 4 blocks of pain-related (B) and non-pain words (C) were presented in an ABAC design. Each 30-second experimental block was interspersed with 30 seconds of "REST" (A) displayed on the screen and block order was counterbalanced. In each experimental block, a different word was presented to the subject every 5 seconds with 6 words presented in total. All participants were naive as to the purpose of the experiment.

Although all pain-related and non-pain words used contained similar familiarity, visual, and somatic elements, there may have been differences in the activity level conveyed by the words. Participant instructions were explicit relating to the task that they were to undertake. In particular, participants were asked to generate an explicit memory to each word that should include visual mental images, feelings associated with the memory, and an activity associated with the word and could use either a first- or third-person reference frame. Participants were encouraged to "free think" about what the words meant to them; however, to ensure compliance,

participants were instructed that after the scanning procedure, they would be asked to give specific examples of the episodes retrieved during scanning. When the word "REST" appeared on the screen, participants were informed that they should relax, clear their minds, and disengage from their memory retrieval task.

On completion of the fMRI experiment, the experimenter conducted a post-scan interview. This was to ensure that the task instructions had been met and to assess the context of the memories retrieved. Participants were explicitly asked (i) Did you understand all of the words? (ii) Were there any words that you did not retrieve a memory for? (iii) Was one type of memories more vivid than the other type? (iv) Did any of your memories for the non-pain words have a pain element? (v) Did you find it easier to retrieve one type of memories compared with the other type?

Participants were then presented with cue words and were asked to detail the memory they retrieved for it. The responses were then coded as relating to either a specific event, if a visual mental image accompanied the memory, and, finally, if the memory contained a physical and/or affective association, such as an auditory, tactile nociceptive/noxious, spatial, olfactory, thermal, and movement-related sensation.

Magnetic resonance data were acquired with the use of a 1.5-T SIGNA LX/Nvi neuro-optimized system (General Electric, Milwaukee, WI). Functional MRI was performed with a blood oxygenation level-dependent (BOLD) sensitive T_2*-weighted multislice gradient echo EPI sequence (TE = 40 ms, TR = 3 seconds, flip angle = 90°, FOV = 19 cm, 64 × 64 matrix). Twenty-four contiguous 5-mm thick axial slices were prescribed parallel to the AC-PC line and covered the entire brain. For the purpose of anatomical referencing and visualization of brain activation, a high-resolution, T_1-weighted, 3D inversion recovery prepared gradient echo (IRp-GRASS) sequence was also acquired (TE = 5.4 ms, TR = 12.3 ms, TI = 450 ms, 1.6-mm slice thickness, FOV = 20 cm, 256 × 192 matrix), with 124 axial slices covering the whole brain. Each fMRI paradigm consisted of 8 pairs of alternating OFF (ie, REST) and ON (pain-related or non-pain words) epochs (starting with 30 seconds of OFF), with each epoch lasting 30 seconds in length, giving a total scan time of 8 minutes, 30 seconds. Every 3 seconds, an entire image volume was collected, giving a total of 170 volumes.

Data analysis was carried out with the use of FEAT5 software, (FMRI Expert Analysis Tool; FMRIB Centre, University of Oxford, Oxford, UK) part of the FMRIB Software Library [FSL: www.fmrib.ox.ac.uk/fsl]. The following pre-statistics processing was applied: Motion correction using MCFLIRT[17]; spatial smoothing using a gaussian kernel of FWHM 5 mm; mean-based intensity normalization of all volumes by the same factor; nonlinear high-pass temporal filtering (gaussian-weighted LSF straight line fitting, with σ = 60 seconds). Statistical analysis was carried out with the use of FILM (FMRIB's Improved Linear Model) with local autocorrelation correction of the data (non-linear spatial smoothing and prewhitening).[33,38] Two covariates were analyzed corresponding to the 2 experimental conditions "pain-related" (P - rest) and "non-pain" (N - rest) words. To determine where in the brain activation related to the processing of pain-related words (P) was greater than that of non-pain words (N), a *t* test was performed between (P) and (N) [ie, (P - rest) − (N - rest)]. Similarly, to determine activations related to the processing of only the non-pain words the opposite *t* test was performed [ie, (N - rest) − (P - rest)]. Mixed-effects group analysis (also known as random effects) was carried out with the use of FEAT5 software with statistic images thresholded by using clusters determined by $Z = 1.8$, $P < .05$ (corrected for multiple comparisons) after being transformed into the stereotaxic space of the Montreal Neurological Institute (MNI), using FLIRT [FMRIB's Linear Image Registration Tool[17]]. All results are rendered on a MNI standard brain surface.

Post hoc analyses and graphs were generated for those regions activated during the contrast of pain-related versus non-pain words. Individual masks were created for caudal ACC (BA32′) and IFG (BA44). The height of the activation under each condition (β) in these areas was analyzed using Featquery [part of FSL: www.fmrib.ox.ac.uk/fsl], which produces a percentage BOLD signal change for that region associated with the experimental condition. A *t* test was performed to confirm significant differences in the extent of signal change within each region during the experimental conditions.

Four participants were left-handed (LH). To examine possible confounds through their inclusion in the analysis, a random-effects analysis was conducted between all 14 participants (LH and RH) and 10 right-handed (RH) participants on the previous contrasts, main effect of task, pain-related versus non-pain words, and non-pain versus pain-related words. No significant difference was found (at the uncorrected threshold of $Z = 1.8$, $P = 1$). We therefore chose to include our left-handed participants within the random-effects analysis rather than excluding these volunteers.

Results

Verbal Post-Scan Reports

Post-scan questioning revealed that non-pain words did not invoke any pain-related memories, pain-related mental images, or pain-related somatic associations. In response to questioning, all participants (n = 14) (i) claimed to understand all the words, (ii) retrieved an associated memory for all cue words presented, (iii) claimed equal vividness for both pain-related and non-pain memories, (iv) did not retrieve pain-related memories to non-pain cues, and (v) had no difficulty in retrieving memories to the cued words.

The content of the memories retrieved when cued by pain-related words was 49% contextual in nature and linked specifically to a painful event, 33% contained a visual mental image, and 61% were linked to a physical and/or affective association, 45% of which were solely pain-related; 34% of memories cued by the non-pain words related to a specific event, 68% evoked a mental image, and 41% were linked to a physical and/or affec-

Table 2. Regions Preferentially Activated During Autobiographical Memory Retrieval Versus Rest

Region	Coordinate			Z Score	L/R
	x	y	z		
Inferior frontal gyrus (BA6/44/47)	−40	6	30	5.77	L
Medial superior frontal gyrus	−6	10	66	5.77	L
Pre-SMA	−4	10	44	5.76	L
Cerebellum	−2	8	56	5.71	L
	46	−62	−32	5.68	R
Thalamus	−12	−8	10	5.21	L
Anterior cingulated gyrus (BA32/24)	−12	24	38	5.20	L
Fusiform gyrus (BA37)	−56	−46	−14	5.14	L
Middle temporal gyrus	−58	−46	−14	5.13	L
Anterior insula cortex	−18	10	10	4.62	L
Inferior temporal gyrus	−48	−46	−12	4.59	L
Occipito-temporal junction	−30	−68	32	3.32	L

NOTE: The MNI coordinate and maximum *Z* score of the highest activating cluster in each region are shown.

tive association, which was mainly auditory, tactile, movement-related, olfactory, thermal, affective, or spatial in nature.

Some examples of participant responses to words are listed below.

Bruise

The participant recalled a serious motorbike accident he had been involved in several years previously. He recalled the sound of the bike, the sensation of falling off the bike and sliding along the ground, and feeling and seeing the resulting bruising.

Radiator

The participant recalled standing over her radiator and the sensation of slowly becoming warmer while seeing her room.

Activation of Areas Involved in Silent Reading and Memory Retrieval

The main effect of words versus rest (P + N)/2 vs rest) revealed diffuse activation across the left lateral inferior prefrontal complex (BA6/44/45/47 and insula), anterior cingulate gyrus, left thalamus, pre-supplementary motor area (pre-SMA), left medial superior frontal gyrus, left middle temporal gyrus, left posterior fusiform and inferior temporal gyrus (BA37), and bilateral cerebellum (Table 2).

Pain-Related Words Versus Non-Pain Words

Pain-related words versus non-pain words [(P - rest) − (N - rest)] revealed entirely left-lateralized activation, which occurred predominantly in caudal anterior cingulate gyrus (BA 32′) and inferior frontal gyrus IFG (BA44, extending to BA47/45; Fig 1).

Non-Pain Words Versus Pain-Related Words

Table 3 lists the regions preferentially activated to non-pain versus pain-related words. Activation was seen bilaterally in the posterior cingulate gyrus (BA23/30), bilateral posterior parietal cortex including angular gyrus (BA39), inferior and superior parietal lobe (BA40/7), and left fusiform gyrus.

Relative Contributions of the ACC and IFG in Generating Memories to Pain-Related Words

Graphs of percentage BOLD signal change for the contrast of [(P - rest) − (N - rest)] revealed significant positive activation from baseline under the different conditions analyzed by *t*-test pairwise comparison, (Fig 2). The caudal anterior cingulate (BA32′), although responsive to non-pain words, was activated significantly more by pain-related words ($P = .017$). The IFG (BA44) demonstrated the greatest signal difference between pain-

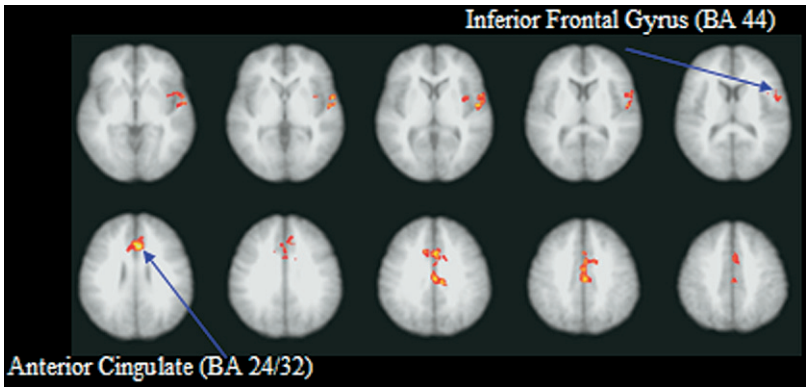

Figure 1. Activation map of the regions preferentially activated by the retrieval of pain-related memories vs non-pain memories [ie, (P - rest) − (N - rest)]. Axial slices (at 4-mm spacing) are shown in radiological convention (images on the left side of the figure correspond to the right side of the brain). The MNI coordinate and maximum *Z* score of the highest activating cluster in each region are ACC (BA32′) $x = -2$, $y = 26$, $z = 28$ $Z = 3.42$, and IFG (BA44) $x = -56$, $y = 8$, $z = 6$, Z = 2.95. BA, Brodmann area).

Table 3. Regions Preferentially Activated During the Contrast of Non-Pain Memory Retrieval Versus Pain-Related Memory Retrieval

Region	Coordinate			Z Score	L/R
	x	y	z		
Fusiform gyrus (BA37)	−32	−42	−18	4.42	L
Occipital-temporal junction (BA39/19)	−32	−78	34	3.86	L
Posterior cingulate gyrus (BA30/23)	4	−56	12	3.84	R
	−4	−60	6	3.59	L
Lingual gyrus (BA18/19)	−8	−48	2	3.57	L
	6	−52	4	3.29	R

NOTE: The MNI coordinate and maximum *Z* score of the highest activating cluster in each region are shown.

related and non-pain words ($P = .008$) in favor of pain-related words.

Discussion

The aim of the current study was to investigate what effect retrieving pain-related memories, cued by pain-related words, has on the pain matrix. Activation in response to memories triggered by pain-related words versus non-pain words were left lateralized to caudal ACC (BA32′) and IFG (BA44). Activation of the caudal ACC (BA32′) supports our hypothesis that in the absence of peripheral sensory stimulation, recalling previous painful episodes cued by pain-related words can activate certain structures of the pain matrix corresponding to the cognitive-evaluative dimension of the pain experience.[37]

Autobiographical Memory Retrieval

The main effect of task (ie, all words vs rest), revealed left-lateralized activation in regions previously identified in the silent reading of words and semantic meaning, namely, lateral inferior precentral complex (incorporating anterior insula and inferior frontal cortex), anterior cingulate gyrus, and superior and middle temporal gyrus extending into the posterior fusiform gyrus.[31] However, areas consistently activated in studies of autobiographical memory such as medial and lateral temporal lobe, hippocampus, and retrosplenial/cingulate regions[22] were absent. The use of rest as a control condition could explain this finding. Stark and Squire[34] demonstrated that areas activated during autobiographical memory retrieval are also active during rest. Furthermore, to mimic the strategy that patients use completing self-report measures, a naturalistic approach to memory generation was used. Unlike other studies of autobiographical memory, participants had not created personal cues for memory retrieval during scanning, which may have affected the activations found.[22]

Areas preferentially activated to non-pain versus pain-related words were bilateral posterior cingulate gyrus (BA23/30), bilateral posterior parietal cortex including the angular gyrus (BA39) inferior and superior parietal lobe (BA40 and 7), and the left fusiform gyrus. Previous studies have implicated the left fusiform gyrus, posterior cingulate, right superior and inferior parietal lobe in mental image generation and visuo-spatial processing.[6] The results of the post-scan interview support this explanation, as they revealed a bias toward creating mental images for non-pain words (Table 3).

Autobiographical Memory Retrieval and the Pain Matrix

IFG is not associated with the pain matrix, and, as such, we had no prediction regarding its involvement in this study. However, it clearly had a differential response to recalling memories cued by pain-related words as revealed by a subsequent analysis examining the magnitude of the response to pain-related versus non-pain

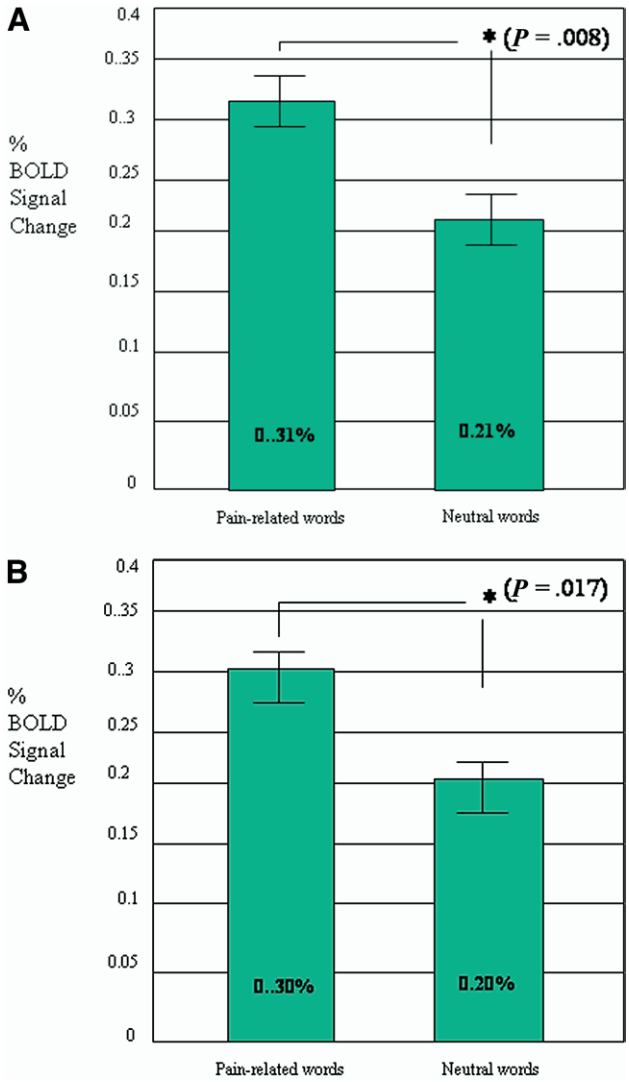

Figure 2. Post hoc graphs generated for **A,** IFG, and **B,** ACC demonstrating mean percentage BOLD signal change in both task conditions. A subsequent *t* test determined the magnitude of the difference, demonstrated as *P* values.

words in caudal ACC (BA32′) and IFG (BA44). Although caudal ACC was activated more by pain-related words ($P = .017$), the greatest difference in the magnitude of response occurred in IFG ($P = .008$).

Activations in both IFG (BA44) and caudal ACC (BA32′) have been found in pain paradigms both with and without noxious sensory stimulation.[21,27,28] For example, Derbyshire et al[7] found caudal ACC (BA32′) activation during 3 experimental conditions, physically induced pain, hypnotically induced pain, and imagined pain. These findings, when considered with those of the present study, demonstrate that the ACC (BA32′) is activated by actual noxious physical stimulation, pain that is mentally generated hypnotically, through imagination or memory retrieval.

The associative model of word processing identified by Hauk et al[16] may provide one explanation for our current findings. This model assumes that neural assemblies responsible for the processing of word stimuli are located in brain structures that are related to word meaning. The findings of the current study, Derbyshire et al,[7] and Hauk et al[16] indicate that the ACC (BA32′), as a component of the cognitive-evaluative dimension of the pain matrix, may mediate all types of pain information, even in the absence of actual physical noxious stimulation. One possible explanation for this is that neural assemblies responsible for the processing of pain-related information, whether internally or externally generated, are located within the cognitive division of the ACC (BA32′).

The location and accessibility of pain-related neural assemblies may provide insight into factors that maintain chronic pain conditions. For example, Flor et al[13] proposed that activation of pain-related cell assemblies create a painful experience in the absence of peripheral sensory stimulation. In chronic pain populations, who display sensitivity to non-painful pain-related stimuli, accessing pain-related neural assemblies may maintain painful conditions or create other maladaptive illness behaviors.[11-13,20,29]

Alternative Viewpoint: Semantic Processing

An alternative interpretation of the current findings considers the semantic processing of the task stimuli. Activation of the ACC (BA32′) has been demonstrated in non–pain-related cognitive tasks,[8] and activation of inferior prefrontal cortex (IPC, BA47/45/44) has been demonstrated in several studies of semantic and phonological processing.[9,30,35] Furthermore, Greenberg et al[15] compared activations for semantic and autobiographical memory retrieval tasks and demonstrated IFG activation in both conditions, but with a more prolonged duration of activation for the semantic task. The present study only used autobiographical memory retrieval; however, the cues presented were not personalized to the individual participant. In the current study, the greatest difference in BOLD signal occurred in the left IFG, suggesting differential semantic and phonological processing of the task stimuli used to cue the recollection of previously painful events.

Differential semantic processing was demonstrated by Osaka et al,[27] who reported activation of the IFG (BA45/44) and caudal ACC (BA32′) when participants were instructed to imagine unpleasant pain and form unpleasant mental images corresponding to acoustically presented Japanese onomatopoeia words (words where the sound of the word helps to suggest its meaning, for example, "butterflies in the stomach"). The authors claimed that because the IFG activation occurred next to Broca's area (BA44) this demonstrates that pain information is being retrieved from long-term memory stores through a semantic retrieval process. The lack of a semantic control task, however, means that these activations cannot be attributed solely to the retrieval of pain information but instead to the processing of words versus nonsense syllables.

Differential semantic processing can occur when there is a disparity in the strength of semantic associations to word stimuli and in relation to the current study, how these semantic associations relate to the pain experience. Behavioral studies have found decreases in task performance[5] and neuroimaging studies have found increases in activation of the left IFG[32] for the retrieval of words that have been processed with weak semantic associations. In relation to the current findings, this could imply that compared with non-pain words, pain-related words had not previously been deeply encoded. However, the distinctive experience of pain makes this seem unlikely and instead, pain-related words may convey more abstract meaning, resulting in weaker or more limited associations to pain, in a pain-free population. When retrieving a previously painful experience, limited associations may have meant that participants had greater difficulty in selecting the target experience from other competing alternatives, a process also demonstrated to increase activation of left IFG (BA45/47).[35] Furthermore, to ensure task efficacy, participants may have maintained the word in working memory through phonologically based temporary storage. This is a process associated with increased activation of left IFG (BA44).[9]

The difference in the magnitude of response between pain-related and non-pain words in the left IFG may well reflect the semantic processing of the word cues. However, the activation found for the caudal ACC, a region known to be involved in processes of cognitive load,[7] although significant, was more discreet. As an area also known for the processing of internally generated pain experiences,[7] this finding may demonstrate that the ACC can mediate the pain element of the retrieved pain memories.

Limitations and Future Directions

There are 2 main limitations to the current study. First, no objective behavioral data were collected in synchronous with the fMRI data. However, verification techniques are limited for autobiographical memory due to its very subjective nature. The inclusion of verbal post-scan reports did provide behavioral data that indicated

that participants complied with task instructions and did not experience difficulty in recalling past events. Second, the semantic categories may have been too dissimilar. Recalling past pain experiences may contain additional affective components that were not examined here. Furthermore, pain words can be ranked in relation to each other in a way that non-pain words cannot. This could also be examined by including affective words that can be ranked, for example, happy, joy, ecstatic. Future combined analysis of fMRI and behavioral data, containing pain-related and affective word stimuli, will enable us to address these issues.

In conclusion, these findings suggest that in pain-free individuals, the IFG and a component of the pain matrix, specifically the ACC (BA32′) form a pain-processing network of higher-order brain structures involved in the cognitive reappraisal of a painful event triggered through pain-related words. The differential activation of the left IFG (BA44) implies that the recollection of the sensory experience of pain in pain-free individuals may require greater semantic processing of the cue word. The application of the current paradigm in a chronic pain population will determine if, with stronger associations to pain, activation of the left IFG is decreased and furthermore if chronic pain patients recreate a physically painful experience, through the sensory-discriminative components of the pain matrix, when recalling previously painful experiences.[35]

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References

1. Apkarian AV, Bushnell MC, Treede R, Zubieta J: Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9:463-484, 2005

2. Bornhovd K, Quante M, Glauche V, Bromm B, Weiller C, Buchel C: Painful stimuli evoke different stimulus-response functions in amygdala, prefrontal, insula and somatosensory cortex: A single-trial fMRI study. Brain 125:1326-1336, 2002

3. Brooks J, Tracey I: From nociception to pain perception: Imaging the spinal supraspinal pathways. J Anat 207:19-33, 2005

4. Conway M: Sensory-perceptual episodic memory and its context: Autobiographical memory. Philos Trans R Soc Lond B Biol Sci 356:1375-1384, 2001

5. Craik FIM, Tulving E: Depth of processing and the retention of words in episodic memory. J Exp Psychol Gen 104: 268-294, 1975

6. D'Esposito M, Detre JA, Aguirre GK, Stallcup M, Alsop DC, Tippet LJ, Farah MJ: A functional MRI study of mental image generation. Neuropsychologia 35:725-730, 1997

7. Derbyshire SWG, Whalley MG, Stenger VA, Oakley DA: Cerebral activation during hypnotically induced and imagined pain. Neuroimage 23:392-401, 2004

8. Devinsky O, Morrell MJ, Vogt BA: Contributions of anterior cingulate cortex to behaviour. Brain 118:279-306, 1995

9. Devlin JT, Matthews PM, Rushworth MFS: Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. J Cogn Neurosci 15:71-84, 2003

10. Edwards LC, Pearce SA: Word completion in chronic pain: Evidence for schematic representation of pain? J Abnorm Psychol 103:379-382, 1994

11. Flor H, Birbaumer N, Schugens MM, Lutzenberger W: Symptom-specific psychophysiological responses in chronic pain patients. Psychophysiology 29:452-460, 1992

12. Flor H, Braun C, Elbert T, Birbaumer N: Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neurosci Lett 224:5-8, 1997a

13. Flor H, Knost B, Birbaumer N: Processing of pain- and body-related verbal material in chronic pain patients: Central and peripheral correlates. Pain 73:413-421, 1997b

14. Gilboa A: Autobiographical and episodic memory: One and the same? Evidence from prefrontal activation in neuroimaging studies. Neuropsychologia 42:1336-1349, 2004

15. Greenberg DL, Rice HJ, Cooper JJ, Cabeza R, Rubin DC, LaBar KS: Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. Neuropsychologia 43:659-674, 2005

16. Hauk O, Johnsrude I, Pulvermuller F: Somatotopic representation of action words in human motor and premotor cortex. Neuron 41:301-307, 2004

17. Jenkinson M, Smith S: A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143-156, 2001

18. Kucera H, Francis WN: Computational Analysis of Present Day American English. Providence, RI, Brown University Press, 1967

19. Leventhal EA: Aging and the perception of illness. Res Aging 6:119-135, 1984

20. Lutzenberger W, Flor H, Birbaumer N: Enhanced dimensional complexity of the EEG during memory for personal pain in chronic pain patients. Neurosci Lett 226:167-170, 1997

21. Maihofner C, Forster C, Birklein F, Neudorfer B, Handwerker HO: Brain processing during mechanical hyperalgesia in complex regional pain syndrome: A functional MRI study. Pain 114:93-103, 2005

22. Maguire EA: Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci 356:1441-1451, 2001

23. Meagher MW, Arnau RC, Rhudy JL: Pain and emotion: Effects of affective picture modulation. Psychosom Med 63: 79-90, 2001

24. Melzack R, Katz J: Pain measurement in persons in pain,

in, Wall PD, Melzack R (eds): Textbook of Pain. 3rd ed. Edinburgh, UK: Churchill Livingstone, 1994, pp 337-351

25. Morley S: Vivid memory for 'everyday' pains. Pain 55:55-62, 1993

26. Oldfield RC: The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97-113, 1971

27. Osaka N, Osaka M, Morishita M, Kondo H, Fukuyama H: A word expressing affective pain activates the anterior cingulate cortex in the human brain: An fMRI study. Behav Brain Res 153:123-127, 2004

28. Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of brain responses to pain: A review and meta-analysis. Neurophysiol Clin 30:263-288, 2000

29. Pincus T, Pearce S, Mcclelland A, Turner-Stokes L: Self-referential selective memory in pain patients. Br J Clin Psychol 32:365-374, 1993

30. Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JDE: Functional specialisation for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage 10:15-35, 1999

31. Price CJ: The anatomy of language: Contributions from functional neuroimaging. J Anat 197:335-359, 2000

32. Raichle ME, Fiez JA, Videen TO, MacLeod AK, Pardo JV, Fox PE, Petersen SE: Practice-related changes in human brain functional anatomy during non-motor learning. Cereb Cortex 4:8-26, 1994

33. Smith S, Brady M: SUSAN: A new approach to low level image processing. Int J Computer Vision 23:45-78, 1997

34. Stark CEL, Squire LR: When zero is not zero: The problem of ambiguous baseline conditions in fMRI. PNAS 98:12760-12766, 2001

35. Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ: Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A re-evaluation. Proc Natl Acad Sci U S A 94:14792-14797, 1997

36. Vogt BA, Nimchinsky EA, Hof PR: Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. J Comp Neurol 359:490-506, 1995

37. Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL: The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry 44:1219-1228, 1998

38. Woolrich MW, Ripley BD, Brady M, Smith S: Temporal autocorrelation in univariate linear modelling of FMRI data. Neuroimage 14:1370-1386, 2001

39. Wright J, Morley S: Autobiographical memory and chronic pain. Br J Clin Psychol 34:255-265, 1995