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Cognitive modulation of pain-related brain responses depends on behavioral strategy

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Abstract

Interactions of pain and cognition have been studied in humans and animals previously, but the relationship between such behavioral interactions and brain activity is unknown. We aimed to show using functional MRI (fMRI) how a cognitively demanding task (Stroop) modulates pain-related brain activations and conversely, how pain modulates attention-related activity. Reaction time data indicated two types of pain responders: subjects in the A group had a faster Stroop reaction time when pain was concomitant to the attention task, while those in the P group had a slower Stroop performance during painful stimulation. fMRI data obtained during Stroop performance with and without noxious stimulation were subjected to region of interest analyses. We first tested whether brain activity during painful median nerve stimulation was modulated by cognitive load. We next tested whether brain activity during the high conflict cognitive task was modulated by pain. Pain-related activity in three regions, primary (S1), and secondary (S2) somatosensory cortices, and anterior insula, was attenuated by cognitive engagement, but this effect was specific to the A group. Pain-related activations in the caudal and rostral anterior cingulate cortex (ACC) and ventroposterior thalamus were not modulated by cognitive load. None of the areas showing attention-related responses, including bilateral dorsolateral prefrontal and posterior parietal cortices, were modulated by pain. These findings suggest that cortical regions associated with pain can be modulated by cognitive strategies. Furthermore, the distinction of behavioral subgroups may relate to cognitive coping strategies taken by patients with chronic pain.

Keywords: Pain; Attention; Imaging; Modulation; Individual; Coping

1. Introduction

Several studies have shown that sensory processes are modulated by cognitive load, especially in the visual system (e.g. Kastner et al., 1998, 1999; Pessoa et al., 2003). In order to activate particular regions of the visual system, a certain level of attention is required, based on the salience of the stimulus and requiring top-down control (Pessoa et al., 2002). Pain is a special case of sensory processing: it is inherently attention-demanding because of its biological salience (Eccleston, 1995; Jones et al., 2003; Melzack, 1999). Despite pain's inherent salience, it may be modulated by a high cognitive load. For instance, Levine et al. (1982) reported increased postsurgical pain when patients directed their attention towards the pain. Conversely, distraction can increase pain threshold and tolerance, and reduce behavioral reactions (Bushnell et al., 1985; McCaul and Haugtvedt, 1982). Cognitive load can affect both pain intensity and unpleasantness ratings, independent of arousal caused by the stimulus (Bushnell et al., 1985; Miron et al., 1989). Overlapping brain networks associated with pain and attention provide a substrate for these behavioral effects. Common nodes include the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPF), and posterior parietal

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cortex (pPar) (Bush et al., 2003; Lazeron et al., 2003; Milham et al., 2001; Ukai et al., 2002; Zysset et al., 2001).

Electrophysiological and brain imaging studies have also demonstrated sensory–cognitive interactions. In monkeys, synchronicity of neuron pairs in secondary somatosensory cortex (S2) was dependent on attentional selection; synchronicity decreased when attention was directed at a visual rather than somatosensory stimulus (Steinmetz et al., 2000). Also, attention directed towards a somatosensory stimulus increased neuronal activity in the monkey primary somatosensory cortex (S1) and S2 (Meftah et al., 2002). Furthermore, there is some evidence that a cognitively demanding task can modulate activity in several regions involved in pain processing, including insular, cingulate, and premotor cortices, thalamus, and cerebellum (Bantick et al., 2002).

Conversely, modulation may be viewed from the perspective of pain affecting cognition. For instance, Dick et al. (2003) showed that mismatch negativity, an early event-related potential (ERP) thought to be involved in attentional orienting responses, is altered in chronic pain patients when pain is reduced by nerve block. Also, cognitive deficits have been reported in some chronic pain patients (Dick et al., 2002; Eccleston et al., 1997; Ozgocmen et al., 2003; Roelofs et al., 2002).

Interactions between pain and cognition, as characterized by behavioral response and brain activity are not well understood. We aimed to show, using functional MRI (fMRI) in healthy subjects who received painful stimuli and simultaneously performed an attention-demanding task, how a cognitively demanding task modulates pain-related brain activations and conversely, how pain modulates attention-related activity. We used the Stroop task since it consistently invokes attentional interference (Bush et al., 1998; MacLeod and MacDonald, 2000). We hypothesized that pain would increase the Stroop reaction time. We further predicted that performance of the cognitive task would attenuate activity in the pain network. We also tested whether acute pain modulates brain regions involved in the Stroop task.

2. Methods

2.1. Subjects

Sixteen healthy, right-handed, adults (8 male, 8 female, 19–34 years old, mean 26.4) participated in the study. All subjects provided informed written consent to procedures approved by the University Health Network Research Ethics Board. All subjects passed a screening session in which they were required to perform a practice Stroop task with 80% accuracy. This screening test lasted less than 3 min, during which the subject was presented stimuli that were rows of x's, rather than words.

2.2. Stroop tasks

The cognitive attention-demanding task was the counting Stroop, a variant of the colour Stroop task (Reisberg et al., 1980; Stroop, 1935). One to four identical words, either emotionally salient, neutral (low conflict), or numbers (high conflict) were presented in a vertical column. Subjects were instructed to respond to the number of words appearing on the screen using a non-ferromagnetic button response box (Rowland Institute at Harvard, Cambridge, MA) with the right hand with buttons corresponding to the responses 1, 2, 3, or 4. The task was implemented in E-prime (Psychology Software Tools, Inc., 2002) and the display was back-projected onto a screen that could be viewed by the subject through a mirror on the MRI head coil.

For the number Stroop, the word, 'one,' 'two,' 'three,' or 'four' was presented one to four times. For the emotional and neutral conditions, words were drawn from a list of 23 (e.g. dying, brutal, and rape for emotional; butter, carpet, and eyebrow for neutral words). The stimuli were presented randomly, with replacement, such that each word was shown an equal number of times, and the order of the words varied. The Stroop task is a well-known task invoking cognitive interference (MacLeod, 1991). In the counting Stroop, the numbers condition provides high interference (Bush et al., 1998), neutral gives low interference, and the emotional Stroop can provide high interference in some patient populations (Williams et al., 1996), but low interference in healthy individuals (Whalen et al., 1998).

Stimuli were presented after 750 ms of a fixation crosshair, and remained for 1250 ms, during which time subjects could respond. Subjects were instructed to respond as quickly as possible while still maintaining good accuracy.

A fourth task condition was a 'rest,' in which a fixation crosshair remained on the screen and subjects did not respond. The four task conditions—emotional, neutral, number, and fixation—were randomly presented for each sensory block, described below. Reaction times (RT) and accuracy were recorded during the scanning sessions.

2.3. Sensory stimuli

Sensory stimuli were elicited by transcutaneous electrical nerve stimulation (TENS) (Empi, Inc., St Paul, MN) of the left median nerve. This protocol has been described previously (Davis et al., 1995; Downar et al., 2003). The TENS device was DC powered and delivered stimuli between 10 and 40 mA in square pulses at 30 pulses/s. The leads were free of loops and had non-magnetic leads. Three conditions of sensory stimuli were used: painful (P), non-painful tingling (T) (paresthesia), or no stimulation (NS). The P and T stimulus intensities were determined by each subject prior to the MR experiment. For pain, the TENS intensity was increased in each subject to achieve a reported level of 6 on an 11-point verbal scale. Each sensory task was 48 s long, and always switched between NS, T, and

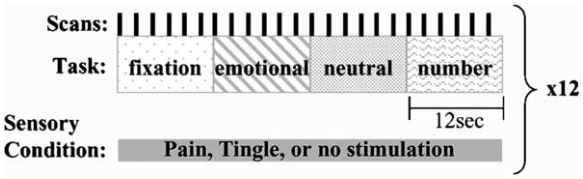

Fig. 1. Block-within-block design. Each 48 s sensory block consisted of pain, no stimulation, or tingle. During each block, the four tasks were randomly presented, with six stimuli presentations per task, each separated by 2 s. Stimulus presentation was for 1.25 s. Each subject underwent two runs of 12 sensory blocks. The four tasks were fixation or counting Stroop with emotional, neutral (low conflict), or number (high conflict) words.

P, in that order. Within each sensory block, each of the tasks was performed, in randomized order. The task protocol is outlined in Fig. 1.

Subjects were told that the sensory stimuli would be changing throughout the scan while they were doing the task. They were not instructed to concentrate on the task or to ignore the sensory stimuli. Data from the NS and P conditions are the focus of this paper; the T data provide a control for non-painful somatosensory input.

2.4. Imaging

Subjects underwent fMRI on a 1.5 T Echospeed MRI system (GE Medical Systems, Milwaukee, WI) fitted with a standard quadrature head coil. Two experimental runs of 9 min, 36 s were performed, with a short rest between runs. A high-resolution three-dimensional anatomic scan of the whole head (124 sagittal slices; 256×256 matrix, 24×24 cm field of view, 1.5×1.07×1.07 mm voxels) was obtained using a T1-weighted 3D spoiled gradient echo (SPGR) sequence (flip angle = 45°, echo time (TE) = 5 ms, repetition time (TR) = 25 ms). Whole brain functional imaging used one-shot gradient echo imaging utilizing a spiral trajectory through *k*-space from 25 axial slices (T2*-weighted images; flip angle = 85°, TE = 40 ms, TR = 2000 ms, 64×64 matrix, 20×20 cm field of view, 3.125×3.125×4 mm voxels). A total of 301 functional volumes (i.e. frames) were acquired for each run and the first three scans were removed to allow signal equilibration.

Brain Voyager 2000 software (version 4.9.6; Brain Innovation b.v. Maastricht) was used for preprocessing and statistical analysis. Details of the imaging, preprocessing, and statistical methodology for thresholding have been described in our previous studies (Downar et al., 2002, 2003). Briefly, preprocessing included resampling the anatomic images to 1×1×1 mm using sinc interpolation, correcting functional data interslice differences based on the time of acquisition, 3D motion correction with sinc interpolation, and resampling images at 3×3×3 mm. Images were spatially normalized into a common stereotaxic space. Linear trends were removed separately for each pixel using a least squares standard method. Data were highpass filtered to remove slow drifts in signal intensity with a period greater than twice the total duration of the four stimulus condition blocks. Spatial smoothing using a Gaussian kernel with 6 mm at full-width half-maximum was also performed.

2.5. Statistical analysis

A general linear model (GLM) analysis of variance was used to analyze task RT data.

A two-part analysis of the functional imaging data was performed. The first part identified regions activated by the noxious stimulus and tested how they were modulated by cognitive load. First, a comparison of P versus NS conditions during fixation was performed in order to determine regions activated by pain. This analysis used a *P*-value set at $P < 0.0001$, with a minimum requirement of 150 contiguous 1 mm^3 voxels activated, which provided a conservative estimate and reduced the likelihood of type 1 error. We have successfully used this approach previously (Downar et al., 2001, 2003). Next, activations identified in this analysis were subjected to a region of interest (ROI) analysis to determine whether performance of the high conflict number Stroop condition significantly modulated the pain-related activity. ROI analyses were corrected for timecourse temporal autocorrelations in order to decrease the probability of type I error (for review, see Woolrich et al., 2001; Worsley et al., 2002). Briefly, correction for serial correlations removes the correlation in time series data, such that each data point is independent of its preceding data point. Because the test with correction for autocorrelations is very stringent and greatly reduces model overestimation, a *P*-value of less than 0.05 was used. For very large activated volumes, a focused central region of the ROI was used.

The second analysis examined whether the attention-related brain regions activated in the interference task were modulated by painful stimulation. To identify brain activity related to high attentional demand, a GLM analysis was performed comparing the number Stroop (high conflict) to the neutral Stroop (low conflict) during the NS condition. ROI's identified from this analysis were further compared for the effect of pain (P versus NS) during the performance of the number Stroop.

3. Results

3.1. Behavioral data

A summary of accuracy and RT for each condition is given in Table 1.

In a group analysis, RT on the number Stroop task (high conflict) was significantly greater than the neutral Stroop (low conflict) (mean difference 32.6 ms; $F(1) = 10.6$, $P < 0.001$). RT for the emotional Stroop was not significantly different than the neutral Stroop (mean difference 9.08 ms; $F(1) = 0.901$, $P = 0.340$).

Table 1
Reaction time (RT) and accuracy (Acc) ± SE for each Stroop task in each sensory condition

	All subjects		A group		P group	
	Acc (%)	RT (ms)	Acc (%)	RT (ms)	Acc (%)	RT (ms)
No stimulation						
Neutral	96 ± 0.7	641.3 ± 6.8	97 ± 0.8	639.1 ± 8.1	95 ± 1.2	644.1 ± 11.7
Number	92 ± 1.0	673.9 ± 7.3	94 ± 1.1	692.8 ± 8.7	90 ± 1.7	649.6 ± 12.4
Emotional	97 ± 0.7	650.4 ± 6.6	96 ± 1.0	641.9 ± 8.4	98 ± 0.8	661.2 ± 10.7
Tingling						
Neutral	98 ± 0.5	661.7 ± 6.6	97 ± 0.8	636.4 ± 7.9	99 ± 0.6	694.4 ± 10.9
Number	92 ± 1.0	690.3 ± 7.5	93 ± 1.2	682.3 ± 9.1	91 ± 1.6	700.6 ± 12.6
Emotional	95 ± 0.8	651.1 ± 7.0	95 ± 1.1	639.6 ± 8.6	96 ± 1.1	665.8 ± 11.5
Painful						
Neutral	96 ± 0.7	644.2 ± 7.0	97 ± 0.8	627.7 ± 7.8	95 ± 1.2	665.4 ± 12.4
Number	93 ± 0.9	674.2 ± 7.3	94 ± 1.2	653.7 ± 8.7	93 ± 1.4	700.6 ± 12.1
Emotional	95 ± 0.7	642.8 ± 7.2	98 ± 0.7	645.3 ± 7.8	93 ± 1.4	639.5 ± 13.0

There was no statistically significant difference in number Stroop RT between the P and NS conditions ($F(1) = 0.001$, $P = 0.975$). However, there was an interesting intersubject variability supported by informal verbal reports given by several subjects—some indicated that they performed better during the pain, while others indicated that the pain affected their performance negatively. Fig. 2 shows that 7 subjects (4 males, 3 females) had significantly longer RTs during pain (649.5 ± 12.3 and 700.5 ± 12.1 ms (mean ± SEM) RT for NS and P, respectively; ($F(1) = 8.699$, $P = 0.003$), while the other 9 subjects (5 females, 4 males) had faster RTs during pain (692.8 ± 8.69 and 653.7 ± 8.76 ms RT for NS and P, respectively; $F(1) = 10.041$, $P = 0.002$) (Fig. 2).

The group whose RT increased during the P condition was assigned the label P, for 'pain dominates,' while the other group was labeled A, for 'attention dominates.' These labels are described in Discussion. Mean accuracy remained above 90% for both groups in all conditions. Because accuracy remained high and traditionally RTs are used to investigate interference responses, we did not use accuracy data further.

3.2. Imaging data

3.2.1. Cognitive modulation of pain activations

A fixed effects GLM analysis of the fixation blocks in the P condition versus the NS condition revealed activations in S1, S2/posterior insula (pIns), caudal ACC, perigenual ACC (pgACC), and ventral posterior (VP) thalamus on the right side (contralateral to stimulation), and anterior insula on the left (ipsilateral) side ($t > 3.8$, $P < 0.0001$, cluster size > 150 voxels) (Fig. 3, Table 2 for Talairach coordinates). It should be noted that a comparison of this GLM in the A and P groups revealed no differences in these pain-related regions.

These regions were then explored using an ROI analysis to test for effects of cognitive modulation on regional activity (ROI's shown in Fig. 4, Table 2). Since the number Stroop has the highest interference, the comparison of fixation and number Stroop was used to analyze pain-attention interactions. It was found that the contralateral S1 and S2/pIns, and ipsilateral aIns were all attenuated significantly or marginally significantly by the Stroop interference task. Post-hoc examination by A or P group designation showed that the effects of attenuation of S1, S2/pIns, and aIns were due to subjects in the A group (Figs. 4 and 5a; see Table 2 for summary of ROI statistics). Table 2 also shows regional modulation by the neutral Stroop task. Notice that while S1 and aIns were also modulated by the neutral Stroop only in the A group, this task did not cause modulation of the S2/pIns region. Also, while cACC showed a trend towards modulation for all subjects by the number Stroop task, this is not seen with the neutral Stroop. Fig. 5b shows the non-significantly modulated regions including pgACC, VP thalamus, and cACC. Notice that while significance was not reached, a similar trend towards modulation for the A, but not P group is seen in these regions.

3.2.2. Pain modulation of cognitive activations

We next tested whether pain modulated the attention/cognition related regions. Comparison of the number Stroop with the neutral Stroop during NS activated

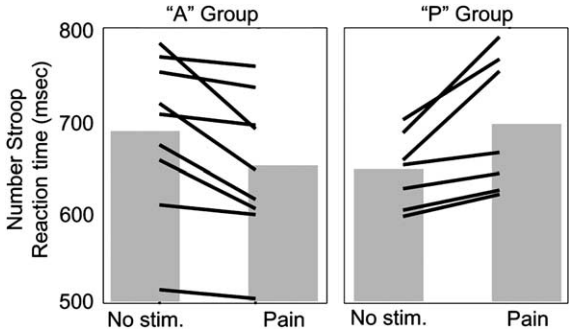

Fig. 2. Reaction time data for the number counting Stroop task with no stimulation or with pain. Lines show data for individual subjects. Bars show group averages. All subjects in the A group decreased their reaction times with pain (left panel), while the subjects in the P group each increased their response time with pain (right panel).

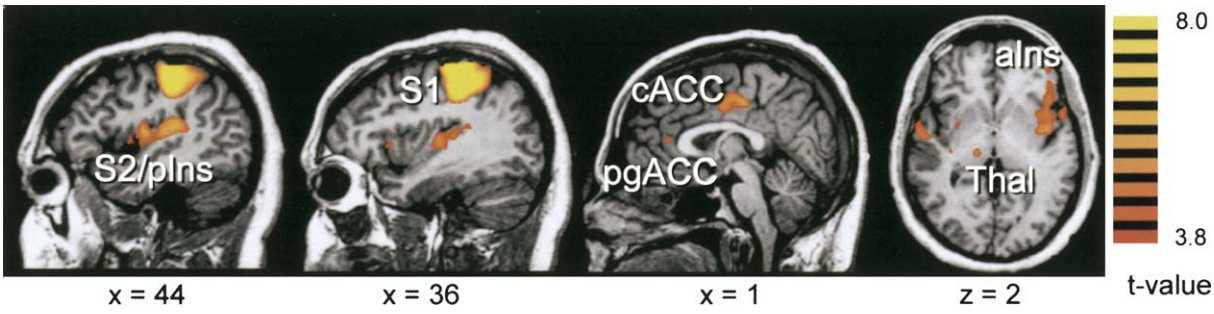

Fig. 3. Activations associated with pain in the fixation condition compared to no stimulation in the fixation condition. Cluster size >150, $t>3.8$ (t-values shown in color bar, right side), $P<0.0001$. Sagittal views show right side of brain; in the axial view, left side of image is right side of brain.

a commonly reported pattern of attention-related regions, including right and left dorsolateral prefrontal cortex (DLPF, Brodmann's area (BA) 9), and right and left posterior parietal cortex (pPar, BA 40/7) (Fig. 6, Table 3 for Talairach coordinates).

ROI's for each of the above regions were analyzed for effects of pain modulation. None of the regions showed significant modulation, although the trend was always a decrease in activity with pain (Fig. 7, Table 3).

3.2.3. The emotional Stroop task

A GLM analysis comparing the emotional to the neutral task in the NS condition revealed only a single activation in posterior cingulate cortex (BA 31, Talairach coordinates −2, −49, 23). Activity in this region was attenuated significantly by pain compared with the NS condition for the entire subject pool ($P<0.05$). However, this modulation was only present in the P group ($P<0.02$), while the A group did not show any modulation ($P>0.53$).

3.2.4. Non-painful somatosensory control

The tingling data was used as a control for non-painful somatosensory stimulation. In a GLM group analysis S1 was the only activation in the contrast fixation T versus fixation NS ($t>3.8$, $P<0.0001$, cluster size >150 voxels). In an additional GLM group analysis of pain-related activations, the fixation P versus fixation T contrast resulted in a map involving identical regions as in fixation P versus fixation NS as listed in Table 2, although the extent of activations were smaller, and pgACC was not activated. No additional regions to Table 2 were activated. We then tested to see whether the cognitive task would cause modulation in S1 during the T condition, and found that there was no significant modulation for the whole subject pool, or for the A or P groups ($P>0.1$ in all cases).

4. Discussion

These data provide insight into the modulating effects of pain and attention on brain activity. Our study indicates that a cognitively demanding task can attenuate pain-related activations in three brain regions: contralateral S1 and S2/pIns, and ipsilateral aIns. These regions are frequently reported as part of the pain network (Casey et al., 1996, 2001; Craig et al., 1996; Davis et al.,

Table 2
ROIs and statistics showing their modulation by the counting Stroop task of the pain response for all subjects, and A and P groups

Region	Task	ROI characteristics				Modulation effect of counting Stroop					
		Volume (mm^3)	Talairach coord			All subjects		A group		P group	
			X	*Y*	*Z*	*t*	*P*	*t*	*P*	*t*	*P*
S1	C	3042	37	−30	54	−1.73	0.085	−2.61	**0.009**	0.20	0.844
	N					−1.17	0.242	−2.56	**0.011**	0.66	0.511
S2/pIns	C	3673	42	−25	16	−2.70	**0.007**	−2.34	**0.019**	−1.33	0.183
	N					−1.16	0.246	−1.37	0.172	−0.13	0.896
aIns	C	3279	−39	2	1	−2.28	**0.022**	−2.44	**0.014**	−0.74	0.462
	N					−2.70	**0.007**	−3.19	**0.001**	−0.45	0.653
CACC	C	1096	5	−6	42	1.85	0.064	1.22	0.223	1.49	0.137
	N					0.40	0.690	−0.24	0.811	0.695	0.487
PgACC	C	165	3	35	14	−0.59	0.557	0.13	0.895	−1.20	0.228
	N					−1.02	0.310	−0.30	0.763	−1.00	0.319
VP Thal	C	680	15	−19	4	0.25	0.799	0.02	0.980	0.56	0.577
	N					−0.35	0.730	−1.295	0.195	0.896	0.370

N, neutral Stroop condition; C, number Stroop condition. Bolded numbers are significant at $P<0.05$. The Talairach coordinate is the center of gravity of the ROI.

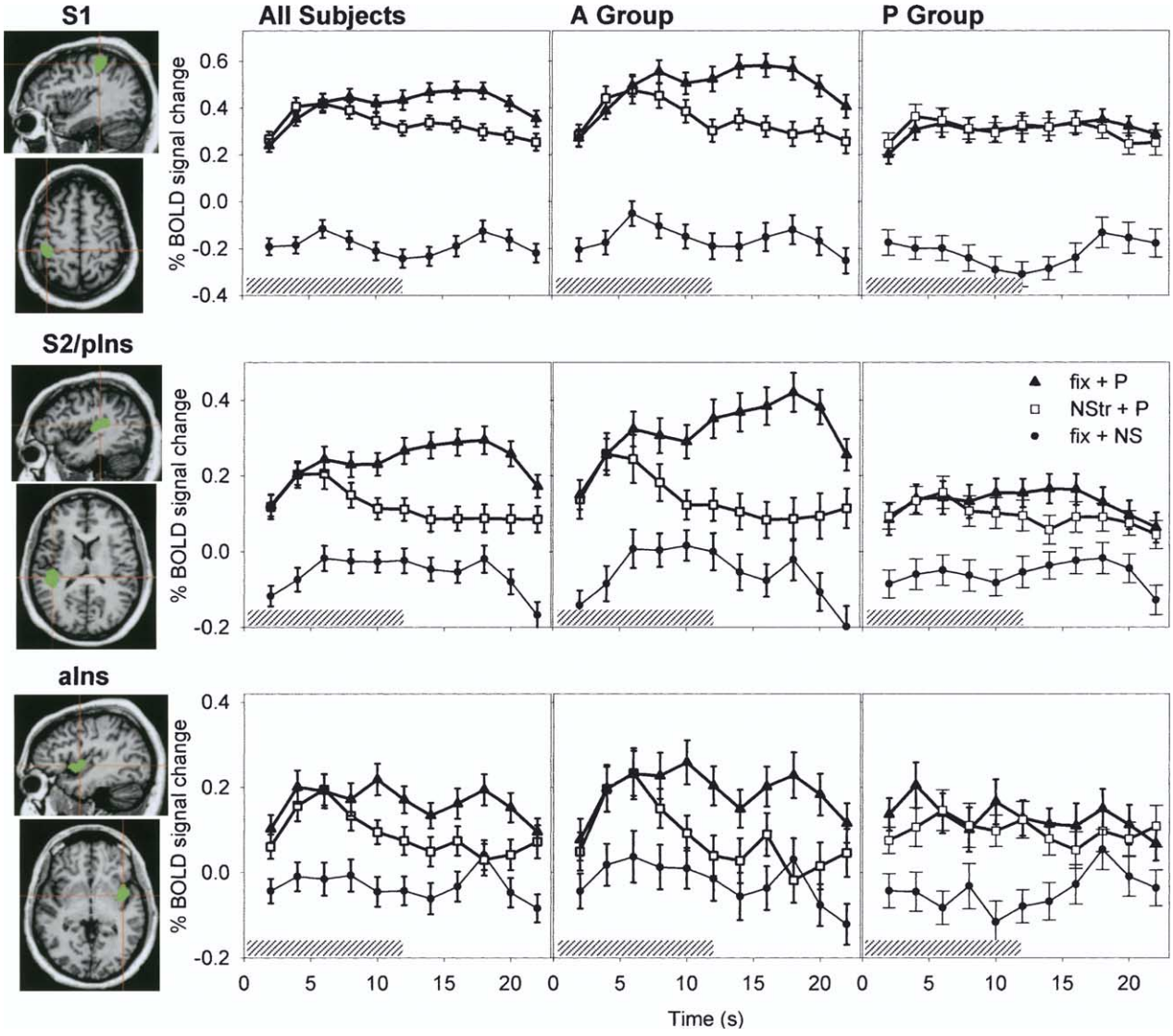

Fig. 4. Region of interest analyses of primary somatosensory cortex S1, secondary somatosensory cortex S2/pIns, and left anterior insula (aIns) showing modulation due to the number counting Stroop in pain as an effect of group. Main effect analysis shows a significant (or near significant in the case of S1) effect of modulation (all subjects), but post hoc analyses show this effect is driven by the A group, while no effect is seen in the P group. The bottom line in the graphs is the fixation with no stimulation (baseline). Percent BOLD signal change (standard error) is based on the average signal across all conditions in the timecourse. The block duration (12 s) is shown by the hatched bar. Legend abbreviations: fix, fixation task; NStr, number (high conflict) counting Stroop task; P, pain; NS, no stimulation. Brain images are radiological convention (left side of figure is right side of brain).

1995, 1997; Derbyshire et al., 1994; Jones et al., 1991; Talbot et al., 1991). Interestingly, this cognitive modulation only occurred in a subgroup of subjects whose Stroop RT was faster during the pain condition (A group). While previous studies have investigated modulation of neural activity by cognitive load (Bantick et al., 2002; Dowman, 2001; Frankenstein et al., 2001; Nakamura et al., 2002; Tracey et al., 2002; Villemure et al., 2003), we show a previously unreported relationship between task behavior and regional brain modulation, distinguishing two groups of subject responses. Our data also indicate that an acute pain stimulus in normal subjects does not interfere with brain activities evoked by cognitively demanding tasks.

The results suggest that the emotional Stroop task requires similar—but not greater—attentional demand as the neutral Stroop task in healthy individuals. Our behavioral findings are consistent with those previously reported (Whalen et al., 1998), with no significant difference in RT between the emotional and neutral tasks. The imaging data indicates only a single region of the brain—the posterior cingulate—has an increased BOLD response compared to the neutral task. Further studies attempting to look at emotional modulation of pain should use a task that more sufficiently causes an emotional response.

It is essential to note that subjects were not instructed to ignore the pain or employ more or less effort in the tasks during the different sensory stimuli blocks. Thus, the data

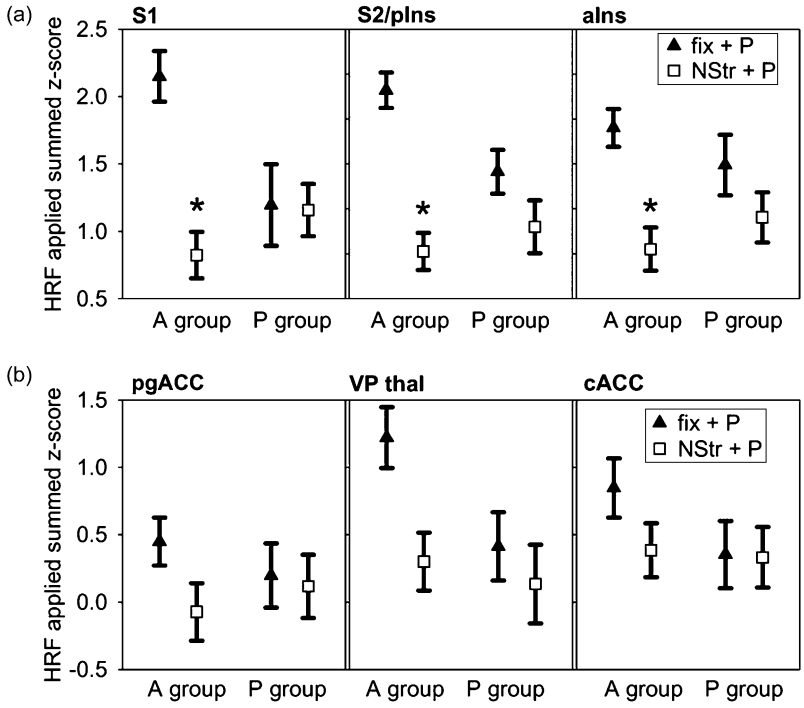

Fig. 5. Regions significantly (a) or non-significantly (b) modulated by the attention-demanding task. Graphs show a physiologically arbitrary score for each condition block to illustrate the effect of modulation in the A and P groups. The mean and standard errors (bars) were derived from the z-scores for each condition with a theoretical hemodynamic response function for the block applied. The hrf-applied z-score is the sum of BOLD signal throughout the stimulation block, shifted for the hemodynamic response. The BOLD signal was z-scored across the entire functional run. $^{*}P<0.05$.

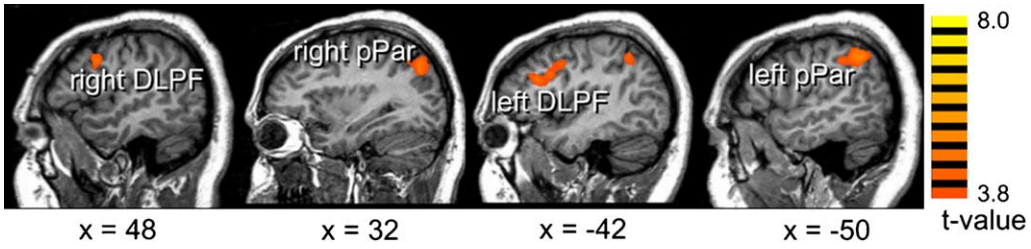

Fig. 6. Activations associated with attention in the number Stroop compared to neutral Stroop in the no stimulation condition. Cluster size >150, $t>3.8$ (t-values shown in color bar), $P<0.0001$.

indicate that subjects freely chose one of two strategies to cope with the pain and perform the attention-demanding task. It seems that the A group focused more on the task during the painful stimulation, which presumably caused a reduction in pain-related activity. In the P group, on the other hand, pain presumably interfered with task performance by diverting attention away from the task. Thus, we have provided evidence that cognitive load can modulate pain-related cortical activity, and also that pain can modulate cognitive performance in healthy subjects.

A limitation in this study is that we do not know whether pain perception per se was reduced in the subjects who

Table 3
ROIs and statistics showing their modulation by pain of the number counting Stroop task for all subjects, and A and P groups

Region	ROI characteristics				Modulation effect of counting stroop					
	Volume (mm^3)	Talairach coord			All subjects		A group		P group	
		X	*Y*	*Z*	t	*P*	*t*	*P*	*t*	*P*
lt dlpf	3126	−40	17	30	−0.63	0.530	−0.04	0.968	−0.88	0.377
rt dlpf	1282	51	10	38	−0.65	0.518	0.30	0.768	−1.25	0.212
lt post par	3089	−47	−47	41	−1.77	0.076	−0.69	0.491	−1.73	0.084
rt post par	1775	35	−64	43	−1.65	0.099	−0.64	0.520	−1.42	0.154

The Talairach coordinate is the center of gravity of the ROI.

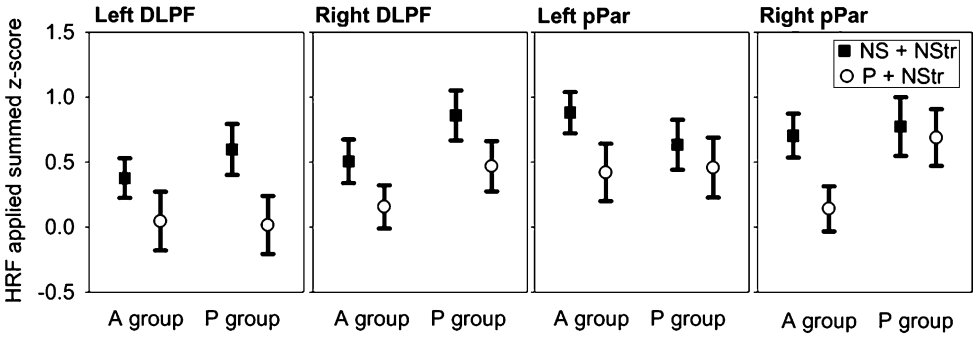

Fig. 7. Modulation of attention-related regions by pain. Regions activated by the high conflict task were not modulated by pain, but a statistical trend towards attenuation is apparent in all regions. Graphs are explained in Fig. 5.

showed modulation of pain activations. Acquiring pain ratings during or after subjects performed the task was purposely avoided to prevent subjects from diverting their attention to the pain for assessment of its intensity. However, previous studies have consistently reported that pain intensity can be attenuated by a distraction task (Bushnell et al., 1985; Frankenstein et al., 2001; Miron et al., 1989; Petrovic et al., 2000; Tracey et al., 2002).

Our findings are a complement to and expansion of previous work on pain modulation by attention, showing modulation in areas of the pain matrix including S1, S2, insula, thalamus, and ACC, either showing decreased activity by distraction away from the pain (Bantick et al., 2002; Petrovic et al., 2000) or increased activity when attention is turned toward the painful stimulus (Hamalainen et al., 2002; Hofbauer et al., 2001; Hsiao et al., 1993; Nakamura et al., 2002). We report in addition to these findings the existence of behaviorally defined subgroups on which attentional modulation was dependent. Furthermore, unlike Bantick et al. (2002), whose design is relevant to acute phasic pain, our study employs a more tonic pain stimulus, and is perhaps more relevant to chronic pain conditions. This design also allowed us to look at the effect of pain on attention-related regions.

Two of the pain regions modulated by attention, S1 and S2/pIns, are typically associated with the sensory-discriminative aspect of pain perception. Although somewhat controversial (Craig, 2003), S1 cortex is currently considered important in sensory localization and intensity discrimination (Bushnell et al., 1999), but may also be involved in pain affect (Hofbauer et al., 2001). Direct stimulation of the dorsal posterior insula, included in the ROI we report (S2/pIns), can induce pain in humans (Ostrowsky et al., 2002). While a small number of S2 neurons are nociceptive (Whitsel et al., 1969), and there is some evidence of a sensory-discriminative component of S2 (Dong et al., 1989, 1994; Glassman, 1994), there is also evidence that S2 may be involved in directing attention toward noxious (Dong et al., 1994) or innocuous somatosensory stimuli (Hamalainen et al., 2002; Hsiao et al., 1993; Johansen-Berg et al., 2000; Meftah et al., 2002; Sinclair and Burton, 1993), suggesting that this region might be involved in both sensory and affect/cognitive elements of pain perception. The third region modulated, the aIns, has been associated with the evaluative-cognitive and affective-motivational aspects of pain (Davis et al., 1998; Nemoto et al., 2003; Peyron et al., 2000; Porro et al., 2002; Rainville et al., 1997). This suggests that cognitive engagement may modulate both sensory-discriminitive and cognitive/affective aspects of pain.

Previous reports have indicated that somatosensory or pain-evoked activity in brainstem and spinal regions can be modulated by changes in attentional states (Bushnell et al., 1984; Dubner, 1988; Dubner et al., 1981; Duncan et al., 1987; Tracey et al., 2002). While we were unable to image these areas with the current protocol, it is plausible that activity in these regions was also modulated, possibly through top-down pathways.

In addition to the effects of cognitive engagement on pain-related activity, we report that pain did not significantly modulate attention-related regional brain activity. Intuitively, since the A group demonstrated modulation of pain-related brain regions—through sustained activation of cognitive networks—we expected the P group to show modulation in the opposite direction (i.e. attenuation of attention/cognition regions via maintenance of activation of the pain network). Because a statistical trend was present, it is possible that modulation can occur, but only in the context of a more taxing cognitive task.

That pain can affect cognition has been shown in several studies examining cognitive deficits in chronic pain (Dick et al., 2002; Kewman et al., 1991; Ozgocmen et al., 2003). In addition to the aforementioned reason, failure to see a modulation of attention-related regions by pain may have resulted because pain recruits attentional resources (Peyron et al., 1999). Thus, rather than attenuating activity in these regions—at least in the P group, to reflect the behavioral effect—there may have been a shift in attention from the task to the pain, necessitating greater cognitive processing.

An important finding here was the distinction of two groups based on behavioral performance with and without painful stimulation. The A and P groups, although identified in a highly controlled, experimental setting, resemble groups of patients with different coping strategies. Coping strategy

has been linked to psychological adjustment and treatment outcome in chronic pain patients (Snow-Turek et al., 1996). In terms of pathological state, coping refers to strategies, behavioral or cognitive/emotional, used to deal with pain in order to improve quality of life. Some chronic pain sufferers rely on others and external influences, while other patients deal with the pain through internal strategies (Snow-Turek et al., 1996). The present work cannot be used to directly understand processing in chronic pain patients because experimental tonic pain in healthy subjects and chronic pain in patients are very different beyond being evoked through similar central pathways. For instance, chronic pain sufferers may have central sensitization, and this may invoke other brain networks not activated in healthy subjects. Nonetheless, these results support the potential for cognitive therapies in the treatment of pain by providing biological credence to cognitive control of pain. Several studies report the benefits of cognitive behavioral therapy (CBT) for pain patients (Lee et al., 2002; Peski-Oosterbaan et al., 1999; Reid et al., 2003; Thomas et al., 2001). The distinction of A and P groups may provide a basis for the finding that some people are unresponsive to CBT or are more likely to relapse after treatment.

Finally, the results in Table 2 indicate that while the number Stroop task invoked greater modulation of pain-related brain regions than the neutral Stroop, this differential effect was modest. It should be noted that both the neutral and number Stroops involve cognitive processing, and so this result is not entirely surprising. Furthermore, the RT difference between the neutral and number Stroop was small (approximately 30 ms) reflecting a modest difference in cognitive load. Future studies will investigate the cognitive modulation of greater cognitive challenges to determine more precisely the interactions between cognitive load and pain processing.

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