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Interactions of Pain Intensity and Cognitive Load: The Brain Stays on Task

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Pain naturally draws one's attention. However, humans are capable of engaging in cognitive tasks while in pain, although it is not known how the brain represents these processes concurrently. There is some evidence for a cortical interaction between pain- and cognitive-related brain activity, but the outcome of this interaction may depend on the relative load imposed by the pain versus the task. Therefore, we used 3 levels of cognitive load (multisource interference task) and 2 levels of pain intensity (median nerve stimulation) to examine how functional magnetic resonance imaging activity in regions identified as pain-related or cognitive-related responds to different combinations of pain intensity and cognitive load. Overall, most pain-related or cognitive-related brain areas showed robust responses with little modulation. However, during the more intense pain, activity in primary sensorimotor cortex, secondary somatosensory cortex/posterior insula, anterior insula, paracentral lobule, caudal anterior cingulate cortex, cerebellum, and supplementary motor area was modestly attenuated by the easy task and in some cases the difficult task. Conversely, cognitive-related activity was not modulated by pain, except when cognitive load was minimal during the control task. These findings support the notion that brain networks supporting pain perception and cognition can be simultaneously active.

Keywords: attention, distraction, fMRI, imaging, individual, modulation

Introduction

Pain draws attention (Eccleston and Crombez 1999), and several lines of evidence suggest that pain processing can interfere with cognitive processes and vice versa. First, several studies have shown a deficit in cognitive ability in people suffering from chronic pain (Kewman and others 1991; Park and others 2001; Apkarian, Sosa, Krauss, and others 2004; Harman and Ruyak 2005). Second, a number of studies have shown that pain perception can be attenuated by cognitive tasks or other distractions, although this is somewhat controversial (for review, see Eccleston 1995). Third, there is some support for the use of coping strategies that employ distraction therapies for chronic pain control (e.g., see Astin 2004). Finally, there is considerable evidence from functional magnetic resonance imaging (fMRI) (Petrovic and others 2000; Frankenstein and others 2001; Bantick and others 2002; Remy and others 2003; Seminowicz and others 2004; Valet and others 2004; Buffington and others 2005; Wiech and others 2005), positron emission tomography (PET) (Petrovic and others 2000; Wiech and others 2005) and electroencephalography (EEG) (Lorenz and Bromm 1997; Dick and others 2003; Babiloni and others 2004; Houlihan and others 2004) studies suggesting that pain- and cognitive-related activity interacts in the brain, possibly because of a reliance on shared neural resources. However, it is not known whether these interactions depend on cognitive load and pain intensity.

Experimental painful stimulation activates a specific set of brain regions that includes the anterior cingulate cortex (ACC), primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, thalamus, and prefrontal cortex (PFC) (Apkarian and others 2005). Similarly, visual cognitive tasks that require a manual response evoke activity in a common set of brain regions (see Fan and others 2003) including the dorsolateral prefrontal cortex (DLPF), posterior parietal cortex (pPar), premotor cortex, insula, and ACC (Bush and others 2003).

In a previous study, we showed that pain-related activity in S1, S2, and insula was attenuated by concurrent engagement in a Stroop task, but that this attenuation was dependent on how subjects engaged in the task while pain was being induced (Seminowicz and others 2004). These results raised the possibility that such an effect was dependent upon the intensity of pain and degree of cognitive load.

In the present study, we examined how the brain balances different loads due to pain intensity and performance difficulty. The aim of the study was to determine how forebrain activity in cognition-related areas changes when pain is present and, conversely, how forebrain activity in pain-related areas changes with the performance of a cognitive task. Furthermore, we determined whether these effects were dependent on pain intensity and/or cognitive load using 2 levels of pain intensity and 3 levels of cognitive load. Our results have implications for understanding the brain's ability to support multiple cognitive and perceptual processes simultaneously.

Methods

Subjects

Twenty-three healthy, pain-free subjects (11 males, 12 females, mean age [standard deviation] 25.6 [4.1]) participated in the study. Each subject gave informed written consent, and the study was approved by the University Health Network research ethics board.

Cognitive Task

The cognitive task was a modified version of the multisource interference task (MSIT; Bush and others 2003), with 3 levels of difficulty. In all trials (all levels), the goal of the task was to identify the number on the screen that was different from the other 2 characters and then press the button corresponding to that number. The MSIT introduces conflict through spatial, size, and flanker features. In the easy task, 2 of the 3 characters were "x," and the position of the number corresponded to the position on the button box (e.g., 1 x x, correct answer is "1"). In the moderate task, flanker and spatial factors were used (e.g., 2 3 3, correct answer is "2"). In the difficult task, flanker, spatial, and size factors were used (e.g., 2 3 2, correct answer is "3"). A fourth task was a motor control tapping, in which subjects hit keys sequentially in response to the position of an asterisk (e.g., * - -, correct answer is "1") (Fig. 1). Because stimuli always appeared in sequential order in the control task, responses were somewhat automatic, requiring minimal cognitive

demand and expressing no cognitive conflict. Stimuli appeared every 1750 ms, were present for 1500 ms, and were then followed by a blank screen for 250 ms. Subjects responded on a magnetic resonance (MR)-compatible button box (Rowland Institute of Harvard, Cambridge, MA), and task stimuli were viewed on a screen through a head coil–mounted mirror.

Experimental Pain

A block design in fMRI studies provides excellent signal/noise compared with an event-related design. A block design for the current study required long periods of combined cognitive task and pain. For this reason, transcutaneous electrical nerve stimulation (TENS) was chosen as the stimulus modality to elicit pain because it can be delivered for a prolonged time without damaging the skin (unlike noxious thermal or mechanical stimuli). Pain was evoked via TENS (EMPI 300 PV) of the left median nerve (Seminowicz and others 2004) using a square wave asymmetric pulse (200 μs) at 35 Hz. Pain intensity was rated on a verbal scale of 0 (no pain) to 100 (extremely intense pain). In each subject, 2 TENS current levels were determined prior to fMRI: a mild level that consistently evoked a pain intensity rating of ~20 and a moderate level that evoked a rating of ~60.

In total, there were 12 conditions, which included all possible combinations of the task (T0 [tapping], T1 [easy], T2 [moderate], T3 [difficult]) and the pain level (P0 [none], P1 [mild], P2 [moderate]) (Fig. 1). For example, the condition with no painful stimulation during the difficult task would be represented as T3P0.

Functional Imaging

Subjects underwent fMRI on a 1.5-T Echospeed magnetic resonance imaging (MRI) system (GE Medical Systems, Milwaukee,WI) fitted with a standard quadrature head coil. Three experimental runs of 9 min and 44 s were performed, with a short rest between runs. A high-resolution three-dimensional (3D) anatomic scan of the whole head (124 sagittal slices; 256 × 256 matrix, 24 × 24 cm field of view [FOV], 1.5 × 1.07 × 1.07 mm voxels) was obtained using a T_1-weighted 3D spoiled gradient echo sequence (flip angle = 45°, echo time [TE] = 5 ms, repetition time [TR] = 25 ms). Whole-brain functional imaging used one-shot spiral gradient echo imaging of 25 axial slices (T_2*-weighted; flip angle = 80°, TE = 40 ms, TR = 2000 ms, 64 × 64 matrix, 20 × 20 cm FOV, 3.125 × 3.125 × 4 mm voxels). A total of 295 functional volumes were acquired for each run; the first 3 scans were removed to allow signal equilibration.

The fMRI experiment employed a block design. During each functional run, 12-s control (tapping, no stimulation) blocks were interleaved with 14-s condition blocks. The order of condition block presentation was randomized within subjects.

Analysis

Behavioral data on the cognitive task were analyzed in SPSS 12.0.1 (SPSS Inc., Chicago, IL) using a repeated-measures general linear model (GLM), with within-subjects factors "task" (4 levels) and "pain" (3 levels). Significant main effects were further evaluated using simple effects with Bonferroni correction for multiple comparisons. This analysis was done with accuracy and reaction time as separate measures.

Brainvoyager QX (Brain Innovation, Maastricht, The Netherlands) versions 1.1.6 and 1.4 were used for preprocessing and data analysis of the functional data, respectively. Preprocessing included, in the following order: motion correction, slice timing correction, linear trend removal, high-pass filtering at 3 cycles per run, and smoothing to 6-mm full width half maximum. Datasets were interpolated to 3 × 3 × 3 mm, aligned to the anatomical image, and transformed to Talairach space. Reported voxels are 1 × 1 × 1 mm. The data were transformed into percent signal with respect to the overall time course for the whole-brain dataset.

In order to identify regions activated by the task and by pain, we performed 2 whole-group, random-effects GLM analyses at a corrected $P < 0.05$ for false discovery rate detection (uncorrected, $P < 0.001$ and a cluster minimum volume of 120 mm^3). The first analysis identified pain-related regions of interest (ROIs) by comparing moderate pain with no stimulation, without cognitive task (i.e., during tapping)—T0P2 versus T0P0. The second identified cognitive-related ROIs by comparing the difficult cognitive task with the tapping task, with no stimulation—T3P0 versus T0P0. For further ROI analysis, a cube of 10 × 10 × 10 mm was drawn around the peak voxel within each ROI to obtain an unbiased sample of the region that could account for intersubject variability. Voxels in the cube that lay outside of the brain were excluded. For subcortical regions, a volume of 5 × 5 × 5 mm was used.

To determine how each ROI was affected by a given task, pain level, or the interaction of task and pain, data from each ROI were submitted to

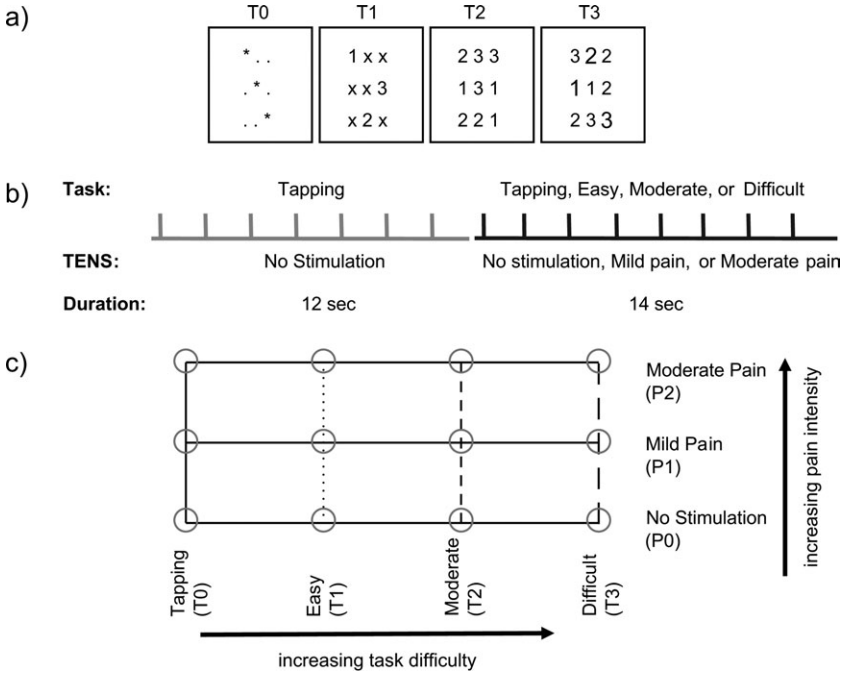

Figure 1. Tasks and fMRI paradigm. (*a*) Examples of 3 sequential trials of each type of task. Descriptions of the task are given in Methods. (*b*) In each trial, a 14-s "condition" block consisting of a task and painful stimulation or no stimulation was preceded by a 12-s "rest" period, during which no stimulation was present and the tapping control task was performed (P0T0). This resulted in the conditions represented by gray circles in (*c*). Each condition was replicated a total of 6 times over 3 runs per subject.

the following 2 analyses. First, for each subject, a single beta value for each of the 12 conditions was calculated for each ROI. Because the entire brain dataset was earlier transformed into relative percent signal, the beta values extracted represent percent signal change. Note, however, that the beta value represents data over the whole predicted hemodynamic response function and not the peak activation. Second, all the extracted beta values were entered into SPSS 12.0.1 (SPSS Inc.) for all further analyses. A repeated-measures GLM was performed with within-subjects factors task (4 levels) and pain (3 levels) for each ROI individually. The results of the GLM allowed us to assess the significance of main effects for task, pain, and the task–pain interaction on the activity of each region. If significance for the main effect was reached, simple-effects tests were performed to further interrogate the effect of each factor. When there was a significant pain-by-task interaction, simple effects for all 12 conditions were performed. All simple effects were subjected to Bonferroni correction for the number of comparisons of interest. The number of comparisons for each test follows: task, 6; stimulation, 3; task-by-pain for pain-related ROIs, 9; task-by-pain for attention-related ROIs, 8. The interactions of interest for the pain-related ROIs include the effect of cognitive load (i.e., task difficulty level) on pain of different levels, whereas those for attention-related ROIs are the effect of pain on a given cognitive load.

We took measures to ensure that our results were based on consistent patterns across subjects. First, we used random-effects analyses to identify the regions of activation, which ensure that the effects were based on between-subject variance and could be extended to the population from which the subjects were drawn (Holmes and Friston 1998). Second, the repeated-measures analysis of variance (ANOVA) ensured that the effects were based on changes within individuals. In order to visualize the data and modulation effects in an efficient manner, we have created profile plots to illustrate the average data for each ROI and each condition. In these plots (e.g., see Fig. 5*b*), asterisks show statistically significant effects of interest. We use these plots to summarize all the ROI data in this study.

Pain Ratings

On a separate day after the initial fMRI session, subjects returned to repeat the experiment outside of the scanner in order to acquire pain ratings. Subjects received the following instructions: "You may be prompted at the end of each task to rate the pain intensity or unpleasantness. Rate the pain over the entire time the stimulus was present. Make your rating quickly, so that you are not giving it too much thought. Perform the task as quickly as possible without making any mistakes." Immediately following each block, subjects were prompted to rate pain intensity or pain unpleasantness or do nothing in the case of a blank screen. The purpose of this last "no rating" condition was to minimize anticipation of a rating. Subjects rated pain intensity and unpleasantness 3 times each for every condition, whereas twice for each condition they gave no rating. For some subjects, TENS current was adjusted slightly to maintain intensity ratings near 60 and 20 for moderate and mild pain, respectively. Data were analyzed using a 2 (pain level) × 4 (task difficulty) repeated-measures ANOVA, with simple effects using Bonferroni correction for multiple comparisons.

Results

Behavioral Results

Reaction time and accuracy data confirmed that the task did in fact have 4 different levels of difficulty, as shown in Figure 2*A*. Both pain and task factors significantly affected reaction time ($F_{2,44} = 10.2$, $P < 0.001$; $F_{3,66} = 403$, $P < 0.001$, for pain and task, respectively), but only task affected accuracy ($F_{2,42} = 0.604$, $P > 0.5$; $F_{3,63} = 4.74$, $P < 0.01$, for pain and task, respectively). Simple effects for task indicated that each task of increasing difficulty had a significantly slower reaction time than the task with the next highest difficulty ($P < 0.01$ in all cases), whereas for accuracy, T1 was significantly poorer than T0 ($P < 0.05$) and T2 significantly poorer than T1 ($P < 0.001$), but T3 and T2 did not significantly differ. For pain, reaction time across all tasks was significantly faster for P2 than P0 ($P < 0.001$). The interaction between pain and task was also significant for reaction time ($F_{6,132} = 4.67$, $P < 0.001$) but not for accuracy ($F_{6,126} = 0.665$, $P > 0.6$). A second repeated-measures GLM was performed to interrogate the pain–task interaction and revealed that pain only affected the reaction times in the tapping motor control task (faster reaction times with pain than with no pain) and not the more difficult cognitive tasks (i.e., T0P1 faster than T0P0; T0P2 faster than T0P0; $P < 0.001$ for both).

Pain Ratings

In this fMRI study, we did not ask subjects to rate pain intensity or unpleasantness during the experiment in order not to have subjects divide their attention between the task and the pain. Subjects from the present study repeated the paradigm outside of the MR scanner and provided pain ratings after each block of task/pain. The main effect for task alone was not significant for pain intensity ratings ($F_{3,66} = 0.35$, $P > 0.78$) or unpleasantness ratings ($F_{3,66} = 0.09$, $P > 0.96$), but the pain level by task interaction was marginally significant for intensity ($F_{3,66} = 2.72$, $P = 0.051$) and significant for unpleasantness ($F_{3,66} = 3.09$, $P < 0.05$). However, analysis of simple effects revealed no significant differences at a given intensity for different tasks. That is, increasing the task difficulty did not affect pain intensity or unpleasantness ratings (Fig. 2*B*).

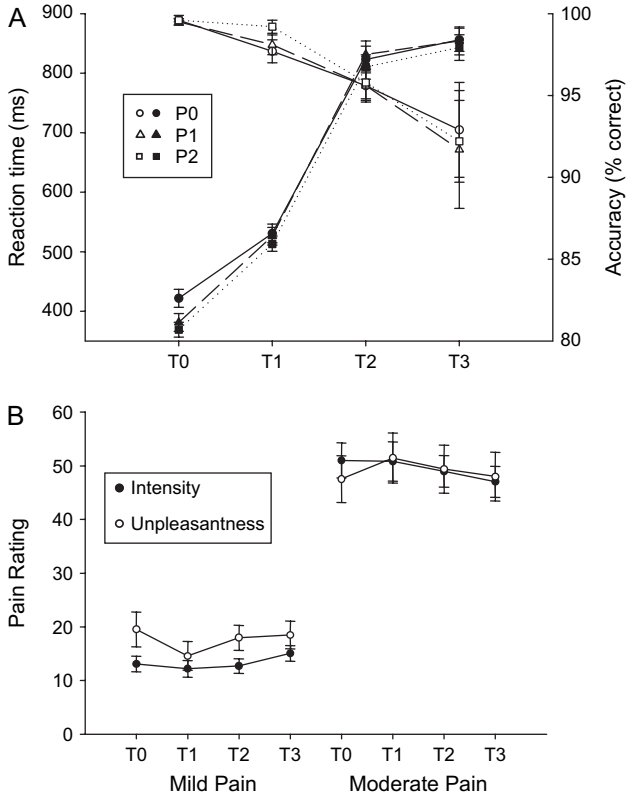

Figure 2. Behavioral data for the MSIT. (*A*) Reaction times (filled symbols) increased and accuracy (open symbols) decreased as task difficulty increased. Pain did not affect reaction time or accuracy, except in the tapping control task (T0), where reaction times were faster with moderate pain (P2) than no pain (P0). (*B*) Pain intensity and unpleasantness ratings (0–100) across MSIT conditions with mild and moderate pain. There were no significant differences in intensity or unpleasantness ratings within moderate or mild pain between any of the task difficulty levels.

Imaging Results

Pain-Related ROIs

The group GLM analysis extracted pain-related brain activations in the contralateral primary somatosensory/motor cortex (S1/M1), S2/posterior insula (S2/pIns), paracentral lobule, caudal anterior cingulate cortex (cACC), ventral motor, mid insula, cerebellum, dorsal and ventral supplementary motor area (SMA), thalamus, midbrain/periaqueductal gray (PAG), and the ipsilateral anterior insula and S2 (Fig. 3). Data from the 13 peak pain-related regions identified from this analysis are shown in Table 1.

Pain-related ROIs were categorized by their response profile to different levels of pain during the tapping (baseline) condition. Three response types were identified (see Fig. 4): 1) a graded response, in which mild pain caused significantly more activity than no stimulation and moderate pain evoked higher activity than mild pain; 2) a pain nonspecific response, in which both mild and moderate pain activated the region, but there was no difference between mild- and moderate-evoked activity; and 3) a high pain-specific response, in which only the higher pain intensity evoked a significant activation. Six pain-related regions showed a graded response: S1/M1, bilateral S2/pIns, ventral SMA, mid insula, and paracentral lobe (see Table 1). Six regions had a high pain-specific response: cACC, dorsal SMA, ventral motor, anterior insula, cerebellum, and midbrain/PAG. Only the thalamus had a pain nonspecific response, although this region actually showed a trend for a graded response.

Many of the 13 pain-related ROIs were modulated by task load. That is, collapsed across all levels of pain (P0, P1, P2), there was a parametric response to task, in which increasing task difficulty resulted in a modulation of pain-evoked activity. This effect was found for the contralateral S1/M1, S2/posterior insula, paracentral lobule, cACC, cerebellum and ventral SMA, and ipsilateral anterior insula. In all cases, except for the anterior insula, the modulation effect was in the direction of a reduction of pain-evoked activity during cognitive load. Simple-effects analyses showed that all these modulated ROIs were modulated by the easy task during moderate pain, whereas 4 were modulated by the difficult task during moderate pain. There was relatively little modulation due to task with mild pain and no pain. Figure 5 shows activity in a representative region (sensorimotor cortex) showing timecourse data and a modulation profile. Figure 6 shows modulation profiles for all pain-related regions.

Cognitive-Related ROIs

A total of 21 task-related cognitive ROIs were identified (Fig. 7), 14 of which showed task-related activations, whereas the other 7 showed task-related deactivations. Task-related activations were identified in the bilateral parietal (Brodmann area [BA] 7,

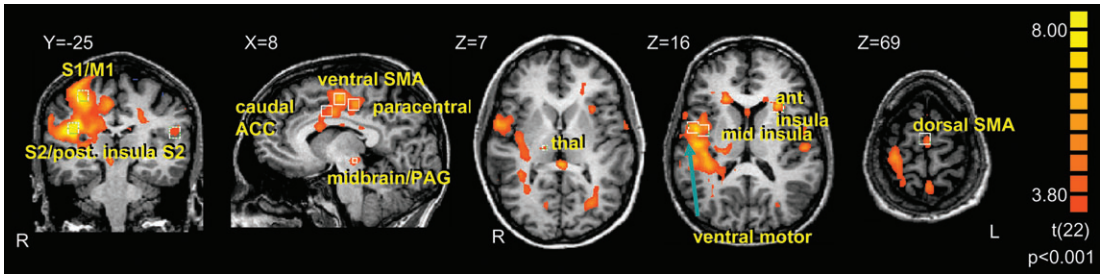

Figure 3. Random-effects GLM (n = 23) showing activations caused by painful stimulation during the tapping motor control versus tapping with no stimulation (P2T0–P0T0). There were no pain-related deactivations. White boxes indicate ROIs. Thal, thalamus.

Table 1
Pain-related ROIs and their responses

ROI	BA	Side	Talairach (x, y, z)	Response type	Main effects from repeated-measures GLM			Post hoc comparisons (vs. T0)								
					Pain ($F_{2,44}$)	Task ($F_{3,66}$)	Pain × task ($F_{6,132}$)	Moderate pain (P2)			Mild pain (P1)			No pain (P0)		
								T1	T2	T3	T1	T2	T3	T1	T2	T3
Regions with significant post hoc tests																
S1/M1	1,2,3,4	R	32, −29, 55	1	78.22*	4.83*	4.40*	D		D						
S2/posterior insula		R	41, −29, 25	1	75.38*	16.54*	2.84*	D		D			D		D	D
Paracentral	6	R	12, −22, 47	1	22.18*	7.26*	4.37*	D		D						
cACC	24	R	4, 3, 41	2	9.07*	3.11*	2.90*	D								
Anterior insula		L	−28, 19, 14	2	14.33*	12.99*	3.25*	D				I	I			
Cerebellum		R	12, −22, 47	2	64.90*	3.78*	7.97*	D		D				D		
Ventral SMA	6	R	9, −9, 52	1	42.24*	1.92	2.87*	D								
Regions with no significant post hoc tests																
Mid insula	13	R	41, −3, 20	1	38.77*	1.15	1.50									
Ventral motor	4/6	R	51, 0, 12	2	52.57*	2.03	1.96									
Thalamus		R	14, −19, 6	3	21.39*	1.06	1.44									
Dorsal SMA	6	R	2, −8, 67	2	8.94*	2.90*	1.48									
S2	43	L	−53, −19, 21	1	13.20*	6.40*	2.13									
Midbrain/PAG		R	8, −23, −5	2	7.15*	1.19	1.95									

Repeated-measures GLM shows the overall effect for each factor and for the interaction factor (pain × task). For those regions where the interaction main effect was significant, post hoc tests of simple effects of interest are indicated by I (increase) and D (decrease). For these post hoc tests, a Bonferroni correction for multiple comparisons was applied (see text). Response types (see Fig. 4 for examples): 1, graded; 2, high pain specific; 3, pain nonspecific. Side, R refers to right hemisphere, contralateral to the pain stimulus; L, left hemisphere. *$P < 0.05$.

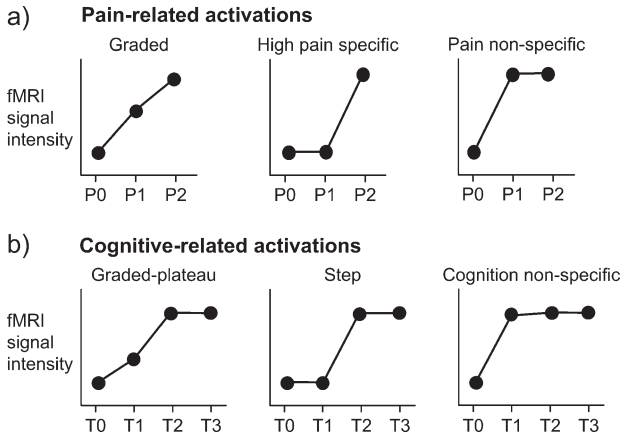

Figure 4. Response type profiles pertaining to pain-related activations (*a*) and cognitive-related activations (*b*). Cognitive-related deactivations had the same response, but in the opposite direction (i.e., activity decreased with increasing task difficulty).

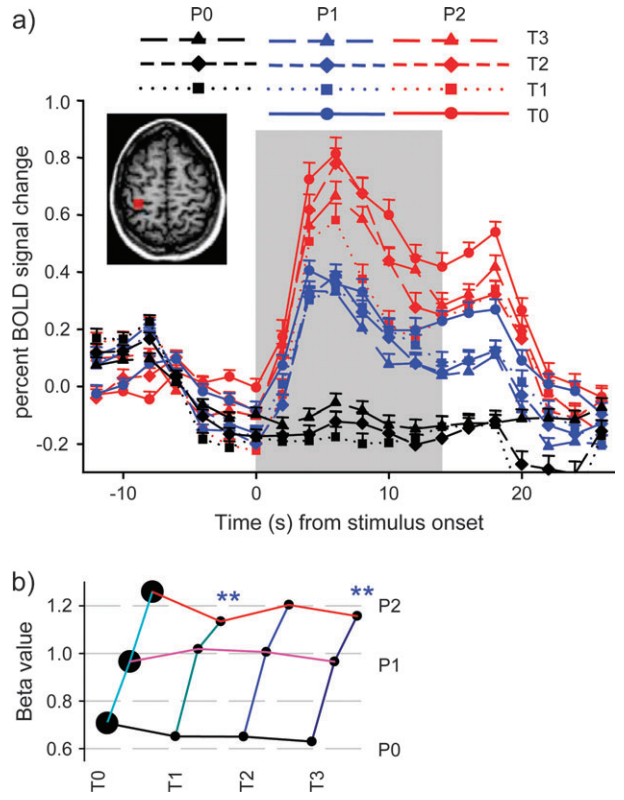

Figure 5. Example of pain and cognitive task effects. (*a*) Event-related average for primary somatosensory/motor cortex. Shaded gray area shows the duration of the condition. ROI is shown in axial brain image. (*b*) Modulation profile for S1/M1. These plots show the influence of pain, cognitive load, and the interaction of pain and cognition. For example, looking only at the cyan line (T0), it is clear that with increasing pain (P2 vs. P1 vs. P0), activity in this ROI increases. This effect is significant across all task difficulty levels (T0–T3). However, the asterisks indicate that compared with P2T0, both P2T1 and P2T3 have significantly ($P < 0.01$) reduced activity. In other words, S1/M1 moderate pain-related activity is significantly reduced by the easy (T1) and difficult (T3) cognitive tasks. Beta values are created from the GLM analysis and represent the estimated fit of the data to the predictive model. Each condition is assigned a beta weight depending on how well brain activity in that area correlates to the onset and duration (normalized by the canonical hemodynamic response function) of that condition.

40), occipital, premotor (BA6), DLPF (BA8, 9, 10), the left SMA, and right anterior insula. Task-related deactivations were observed in the bilateral posterior cingulate and mid/posterior insula, the right S2 and medial frontal cortex (BA10), and the left middle temporal gyrus. Results from the repeated-measures GLM are presented in Tables 2 and 3 for activation and deactivation ROIs, respectively. All ROIs were significantly influenced by task in the omnibus model.

There were 3 different response types for the cognitive ROIs (see Fig. 4). The most common response was a graded increase with a ceiling at the moderate task level (graded plateau). The right anterior insula and right occipital regions had a cognition nonspecific response, in which any level of cognitive load activated the regions. The bilateral DLPF showed a step response, in which the region was only activated during higher cognitive loads. Response types for activations and deactivations are summarized in Tables 2 and 3.

Bilateral occipital cortex, posterior/mid insula, and right S2 were significantly influenced by pain across tasks. The task–pain interaction was significant for all activation ROIs, but only the simple effects of interest were tested and presented. Five regions—bilateral inferior parietal, left superior parietal and dorsal premotor, and right occipital—showed increased activity with the presence of pain. This effect was generally seen only for the motor control tapping condition. For the deactivation ROIs, S2 and right posterior/mid insula were facilitated by pain across all conditions. Both regions overlap with pain-related ROIs, so this finding is not surprising. Note, however, that cognitive ROIs were identified in the absence of pain, and pain ROIs were obtained in the absence of cognitive load. The modulation profiles for all cognitive ROIs are shown in Figure 8.

Discussion

This study demonstrates that pain-evoked and cognitive task-evoked brain activations are quite robust with only modest modulation when subjects are directed to concentrate on the task. The data highlight a complex interaction of pain and cognitive load on brain activity characterized by 4 key experimental findings: 1) more intense pain-evoked activity was more sensitive to attenuation by a cognitive task; 2) the greatest interaction occurred between the higher pain intensity and the easy task; 3) pain did not affect activity in cognitive-related areas of activation except when cognitive load is minimal; and 4) 3 response profile types characterized the forebrain responses to increasing pain intensity or increasing task difficulty, but modulation effects were not restricted to a particular type.

Unique Features of the Study Design

For this study, we wished to maximize detection and exploration of pain–cognition interactions, and so we used a somewhat different experimental approach and design compared with several previous studies examining pain–cognition interactions.

First, in previous studies of pain–cognition interactions, the dual interactions of pain and cognition were tested in a single analysis (Bantick and others 2002; Valet and others 2004; Wiech and others 2005). Although this is a powerful approach, it may preclude examining some regions not involved in a single task. Therefore, we used a different approach in which we first delineated those regions activated with pain or cognitive load and then interrogated how these regions were affected by concomitant pain and cognitive demand.

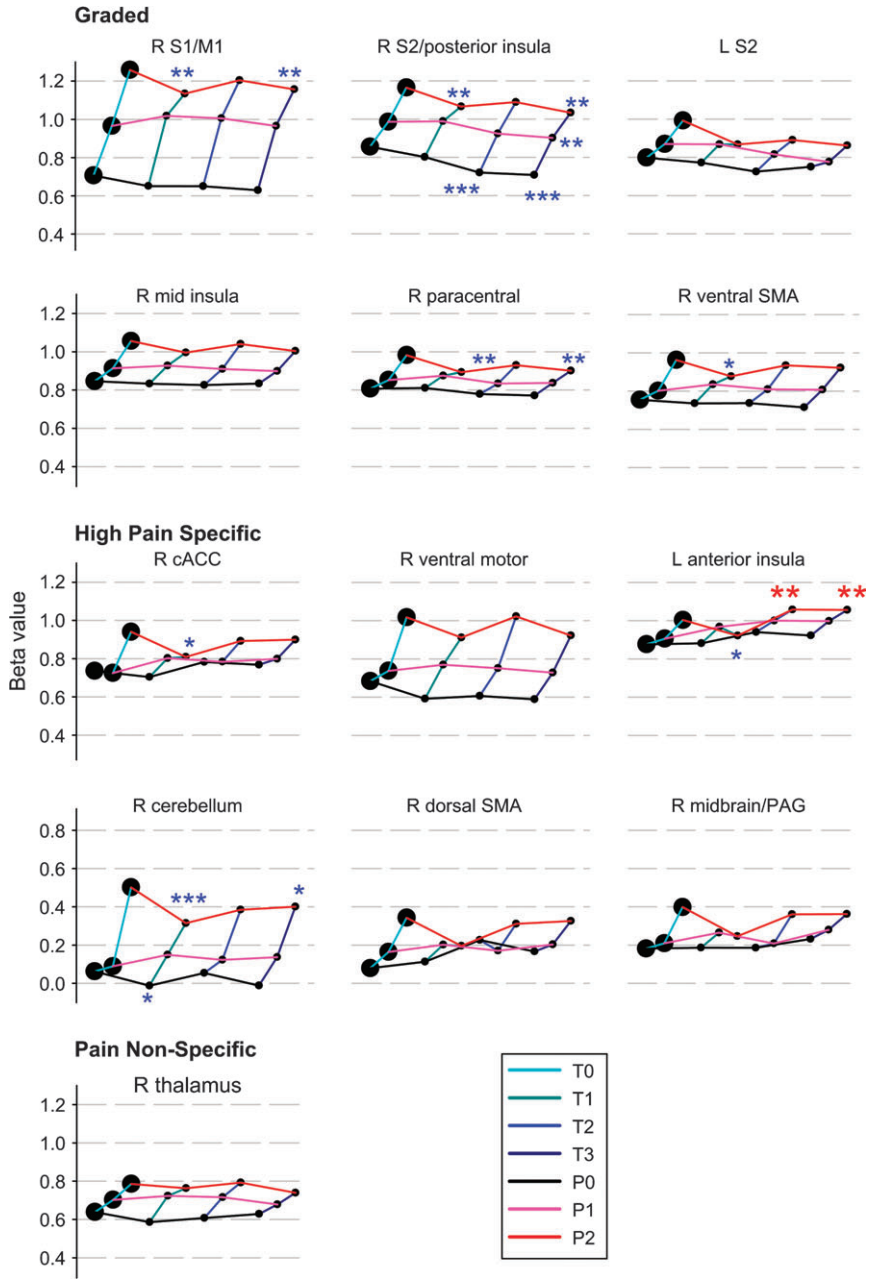

Figure 6. Modulation profiles for pain-related activations. See Figure 5 for an explanation of these plots. Asterisks (*P < 0.05, **P < 0.01, ***P < 0.001) show significant attenuation (blue) or facilitation (red) compared with the T0 condition at the same pain level (see Table 2 to clarify). Large symbols show the response type during the tapping (baseline condition), and regions are grouped by these response types.

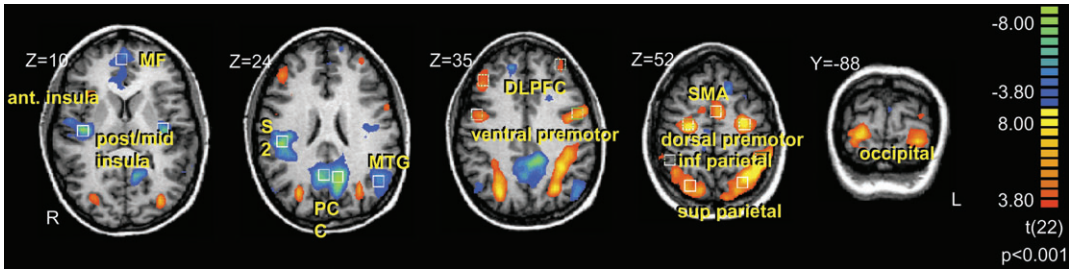

Figure 7. Random-effects GLM (n = 23) showing difficult task during no stimulation versus tapping task with no stimulation (P0T3–P0T0). White boxes indicate ROIs. MF, medial frontal, MTG, middle temporal gyrus, PCC, posterior cingulate cortex.

Table 2
Cognitive-related activations

ROI	BA	Side	Talairach (*x*, *y*, *z*)	Response type	Main effects from repeated-measures GLM			Post hoc comparisons (vs. P0)							
					Task ($F_{3,66}$)	Pain ($F_{2,44}$)	Task × pain ($F_{6,132}$)	Tapping (T0)		Easy (T1)		Moderate (T2)		Difficult (T3)	
								P1	P2	P1	P2	P1	P2	P1	P2
Regions with significant post hoc tests															
Superior parietal	7	L	−27, −61, 47	1	41.51*	0.27	5.71*	I	I						
Inferior parietal	40	R	41, −40, 48	1	24.78*	0.45	5.64*		I	I					
Inferior parietal	40	L	−44, −38, 49	1	44.53*	2.13	4.74*	I							
Dorsal premotor	6	L	−29, −7, 56	1	91.52*	0.95	4.86*	I							
Occipital	18	R	28, −78, −4	3	30.09*	3.95*	4.79*		I						
Regions with no significant post hoc tests															
Occipital	18	L	−35, −79, −1	1	33.08*	3.91*	2.19*								
Superior parietal	7	R	22, −64, 47	1	35.41*	0.15	4.81*								
Dorsal Premotor	6	R	24, −7, 57	1	42.07*	0.27	5.87*								
Ventral Premotor	6	R	46, 3, 33	1	19.92*	0.08	5.39*								
Ventral premotor	6	L	−48, 4, 35	1	26.64*	0.55	5.10*								
DLPF	8/9	R	40, 35, 30	2	11.65*	0.86	6.83*								
DLPF	9/10	L	−32, 50, 30	2	6.06*	1.26	3.63*								
SMA	6	L	−2, 5, 54	1	26.58*	0.44	4.30*								
Anterior Insula		R	32, 19, 15	3	7.71*	1.20	4.07*								

See Table 1 for explanation. Response types (see Fig. 4 for examples): 1, graded plateau; 2, step; 3, cognition nonspecific. *$P < 0.05$.

Table 3
Cognitive-related deactivation ROIs and their responses

ROI	BA	Side	Talairach (*x*, *y*, *z*)	Response type	Main effects from repeated-measures GLM			Post hoc comparisons (vs. P0)							
					Task ($F_{3,66}$)	Pain ($F_{2,44}$)	Task × pain ($F_{6,132}$)	Tapping (T0)		Easy (T1)		Moderate (T2)		Difficult (T3)	
								P1	P2	P1	P2	P1	P2	P1	P2
Regions with significant post hoc tests															
S2		R	42, −23, 24	3	18.10*	126.02*	2.91*	I	I	I	I	I	I	I	I
Posterior/mid insula	13	R	39, −14, 11	3	9.65*	38.44*	4.80*		I	I	I		I	I	I
Regions with no significant post hoc tests															
Posterior/mid insula	13	L	−36, −12, 11	3	17.31*	4.43*	1.02								
Posterior cingulate	31	R	3, −54, 28	2	55.21*	0.33	0.56								
Posterior cingulate	31	L	−10, −56, 25	1	49.93*	1.66	1.03								
Middle temporal gyrus	39	L	−48, 60, 28	2	46.41*	0.24	0.76								
Medial frontal	10	R	3, 52, 11	1	25.59*	0.70	0.92								

See Table 1 for explanation. Response types (see Fig. 4 for examples) 1, graded plateau (negative); 2, step; 3, cognition nonspecific. *$P < 0.05$.

Second, a confound in previous experiments arises from linking brain activity changes to another behavioral measure, pain ratings (Lorenz and Bromm 1997; Petrovic and others 2000; Frankenstein and others 2001; Bantick and others 2002; Dick and others 2003; Remy and others 2003; Babiloni and others 2004; Houlihan and others 2004; Seminowicz and others 2004; Valet and others 2004; Buffington and others 2005; Wiech and others 2005). Because instructions can affect the way in which subjects cope with experimental pain (see Eccleston 1995), simply asking subjects to rate the pain intensity while engaged in a cognitive task changes the experiment from a pain–cognition interaction to a difference between feeling—or believing to feel—different pain intensities. To avoid this confound, we instructed subjects to perform the task quickly and accurately and gave no specific instruction regarding the pain, except that the painful stimulus would be on for short periods during the experiment. Thus, we do not extend our findings by assumption to an effect on pain ratings. Our data show consistent but small changes in pain-related activations from cognitive load, and these need not necessarily directly imply a change in perception. Although we did not collect pain ratings in the fMRI experiment, a subsequent pain assessment in a second session performed outside of the MRI scanner indicated that cognitive load did not significantly affect pain ratings. Moreover, studies in which subjects know they will be required to provide ratings should consider the role of beliefs and expectations (cf., placebo), which are known to contribute to the pain experience and pain-related brain activity (Ploghaus and others 2003; Wager, Rilling, and others 2004; Pariente and others 2005).

Individual Differences in Pain–Cognition Interactions

In order to ensure that the effects we report are consistent across all subjects, we used analyses based on individual changes across the group, rather than fixed-effects analyses which could be driven by a few subjects. The findings herein—both behavioral and physiological—thus reflect consistent effects across subjects. In a previous study, we showed that modulation of pain-related activity was dependent on behavioral strategy: subjects whose performance on the task improved during the pain showed attenuated activity in S1, S2/posterior insula, and ipsilateral (left) anterior insula, whereas those subjects whose performance worsened with pain did not show this effect (Seminowicz and others 2004). In the present study, we did not

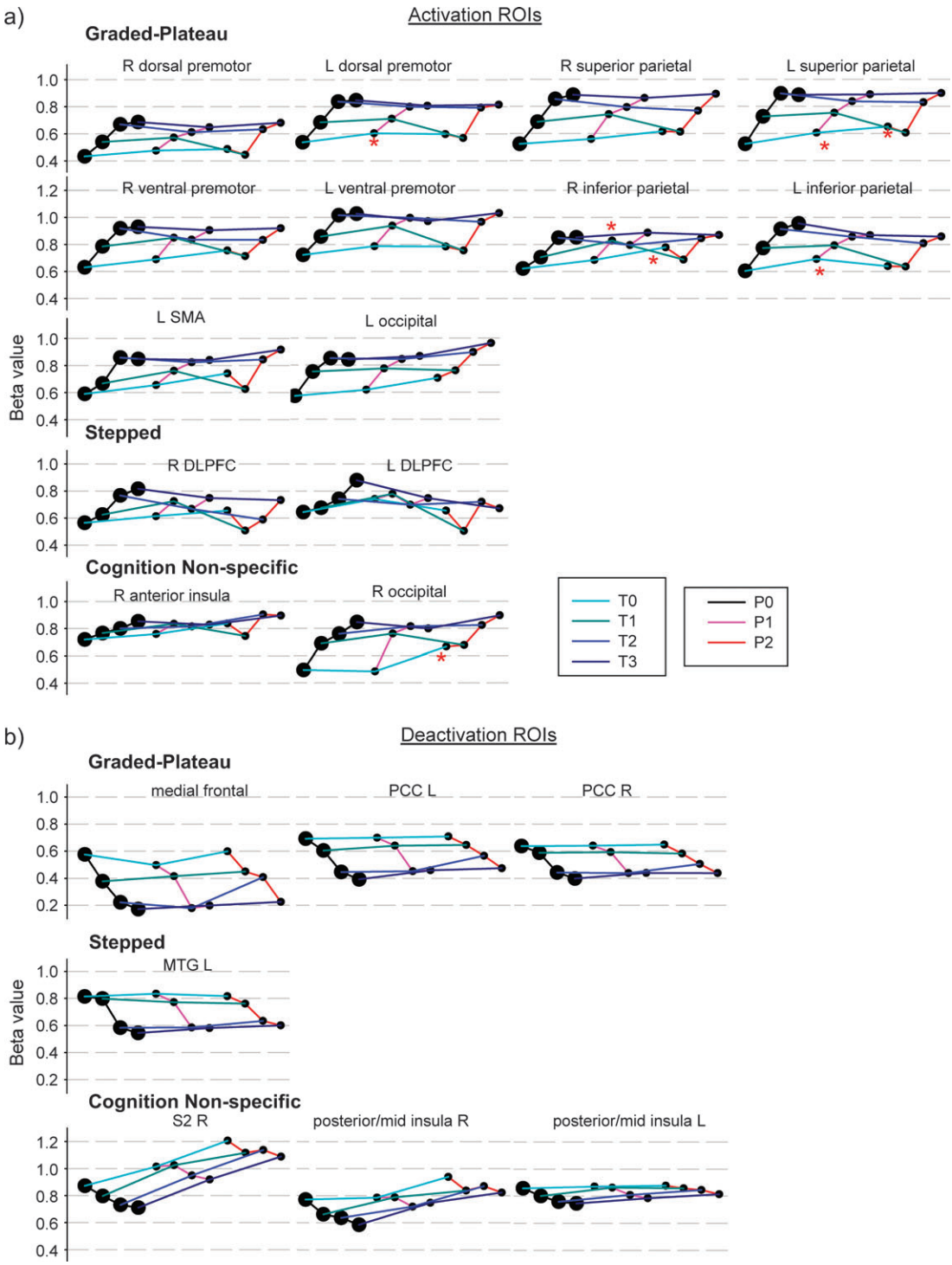

Figure 8. Modulation profiles for cognitive-related activations (*a*) and deactivations (*b*). Asterisks show significant increases in activity. None of the deactivation ROIs was modulated by pain, except right posterior/mid insula and right S2, in which pain significantly increased activity in all task levels. See Tables 2 and 3 to clarify modulations. Large symbols show the response types as described in Tables 2 and 3 during the no stimulation (P0) condition. MTG, middle temporal gyrus, PCC, posterior cingulate cortex.

replicate this finding. In fact, the modulation we describe for pain regions was highly consistent across subjects in the present study. Several differences between the 2 studies, including the type of task (MSIT vs. Stroop) and the duration of the painful stimuli (14 vs. 48 s), which might influence subjects' motivation to escape the pain, could account for these divergent findings.

Pain- and Cognitive-Related Regional Response Profiles

In addition to testing pain–cognition interactions, we were able to show the response profiles of various pain- and cognitive-related regions to different stimulus intensities and cognitive loads, respectively. We found that about half of the pain-related regions showed a graded response, whereby activity from mild pain was significantly greater than no pain and moderate pain

significantly greater than mild. These findings are in line with those of Bornhovd and others (2002), in which laser stimulation resulted in a graded response in S1, S2/pIns, and various areas of insula. Other regions, such as the cACC, ventral motor, anterior insula, cerebellum, dorsal SMA, and midbrain/PAG, were activated significantly only with a moderate intensity of pain. That cACC responds selectively to more intense pain is consistent with previous findings (Davis and others 1997; Buchel and others 2002). On the other hand, Coghill and others (1999) reported that S1, S2/pIns, mid-anterior insula, cerebellum, putamen, thalamus, SMA, and ACC all had graded responses. Other findings are mixed (Derbyshire and others 1997; Porro and others 1998; Ringler and others 2003; Moulton and others 2005), but regions most commonly reported to have a graded response are S1, S2/pIns, and some region of cingulate cortex.

The cognitive task we used activated a network of regions similar to those described in studies involving a comparable cognitive task (Bush and others 2003) and various other studies including attentional control (Woldorff and others 2004) and attentional shift (Wager, Jonides, and Reading 2004). The increase in activity in a frontal–parietal network with increasing cognitive load, we report here, is very similar to that described by Newman and others (2003). Most regions showed a graded plateau response, in which the maximum level of activation was achieved at the moderate cognitive load, even though behavioral results indicate that cognitive load was slightly, but significantly, greater for the difficult task. The bilateral DLPF was only activated at high cognitive demand, indicating that the lower difficulty tasks can be performed without reliance on this prefrontal area.

Effects of Cognitive Load on Pain-Related Activity

Although pain- and cognitive-related activations were robust, there were small but statistically significant modulations in some circumstances. With moderate pain intensity, activity in S1/M1, S2, paracentral lobule, SMA, cACC, anterior insula, and cerebellum was attenuated by the easy and sometimes the difficult cognitive task. Several studies have reported that cognitive engagement reduces pain-related activity (Bushnell and others 1999; Peyron and others 1999; Frankenstein and others 2001; Bantick and others 2002; Tracey and others 2002; Petrovic and others 2004; Seminowicz and others 2004; Valet and others 2004; Wiech and others 2005), especially S1, S2, insula, SMA, and cingulate, consistent with the present findings. These findings could reflect a change in perception. Some of these studies report reductions in pain intensity during a more cognitively demanding task (Bantick and others 2002; Tracey and others 2002; Valet and others 2004). However, these ratings are usually gathered at the end of the experiment, when subjects need to rely on memory of the pain and may have certain expectations of reduced pain in different conditions. We report that cognitive load did not significantly alter pain ratings of unpleasantness or intensity when subjects were asked to rate immediately after a block of painful stimulation.

In the study by Valet and others (2004), performance of a color Stroop task simultaneously with contact heat pain eliminated almost all pain-related activity. In contrast, we found that although activity in several pain-related regions was attenuated, all pain-related areas were nonetheless significantly activated by pain, regardless of the cognitive load present. Our results are consistent with our understanding of the role of these brain areas in pain perception. That is, because of the extremely important biological role of nociceptive pain, it is likely that pain—and pain-related activity—may not be entirely diminished by cognitive disruption.

Effects of Pain on Cognitive-Related Activity and Task Performance

In a commentary article, Eccleston (1995) stated the importance of looking at a 2-way interaction between pain and cognition or cognitive coping strategy. In fact, one of the more intriguing questions in terms of pain–cognition interactions is whether chronic pain affects a person's ability to perform cognitive and related tasks. Several studies have demonstrated that such a cognitive deficit is present with chronic pain (Eccleston and others 1997; de Gier and others 2003; Apkarian, Sosa, Krauss, and others 2004; Harman and Ruyak 2005). Dick and others (2003) demonstrated that patients with chronic pain showed a consistent decrease in mismatch negativity potential, which is related to attentional orienting, when pain was present compared with when it was alleviated by nerve block. Furthermore, reaction times were faster when pain was alleviated. Although an acute pain stimulus did not affect cognitive-related brain activity or task performance in the present study, this does not undercut the likelihood of a persistent painful state affecting cognitive ability or cognitive-related brain activity. In a chronic pain state, patients would have been experiencing a moderate–intense level of pain for a prolonged period of time. This prolonged pain may also be accompanied by fear and anxiety associated with the pain, not typically evoked in a controlled experimental setting. Indeed, several studies have implicated a role for PFC in chronic pain, whereas PFC activation is not consistently reported in healthy subjects experiencing pain (see Apkarian and others 2005). Furthermore, the DLPF may undergo morphological changes with chronic pain (Apkarian, Sosa, Sonty, and others 2004), and because the DLPF is involved in cognition, damage to this area may lead to cognitive deficits.

It may also be the case that the effect of even acute pain on cognition occurs too fast and transiently to be detected with fMRI. Indeed, some EEG studies have shown that pain disrupts some early neural potentials related to attention or attention orienting and thus reflecting a steal of attentional resources by pain (Lorenz and Bromm 1997; Houlihan and others 2004). This type of EEG activity may not be detectable with a vascular-based method like fMRI, particularly in a block design. Another explanation is that our instructions to subjects to perform the task with high performance at all times led to the differences. Similar results were reported by Babiloni and others (2004), where cognitive performance was not affected by the anticipation of painful compared with nonpainful stimulation, and likewise cognitive performance did not affect anticipation-related cortical activity. Interestingly, Houlihan and others (2004) showed that of the different cognitive tasks tested, the strongest interaction between pain and a cognitive-related potential (P3) occurred at the lowest cognitive load, similar to what we report here.

Our behavioral results show that the presence of pain resulted in faster reaction times during the tapping motor control task (T0), but pain did not affect performance on any of the cognitively demanding tasks (T1–T3). Interestingly, our imaging data support this behavioral finding, showing that while performing T0, activity in several cognitive-related regions increased when pain was present, including left premotor and

superior parietal, bilateral inferior parietal, and right occipital cortices. The increased activity in these regions could reflect the faster motor response or, alternatively, an increased alertness and/or arousal. For example, increased arousal from an aversive stimulus facilitates activity in areas responding to an attention task, particularly posterior parietal areas (Tracy and others 2000). pPar is thought to have an important role in arousal and selective and sustained attention (Coull 1998). Moreover, pain can facilitate neural responses related to tactile processing, likely via an alerting mechanism, similar to the effect of directed attention on tactile processing (Ploner and others 2004). Alternatively, these parietal regions may have a role in selective attention to pain (Peyron and others 2000; Duncan and Albanese 2003). Conceivably, these areas are active in directing attention to the pain in the tapping control task, but recruitment of this area during higher cognitive load outweighs this effect.

Overlapping Cortical Regions Involved Independently in Pain and Cognition

Two cortical regions warrant particular consideration: the right S2/posterior insula and the posterior/mid insula. These regions seem to be part of both pain and cognition networks, but respond in opposite directions to different challenges: they were activated during pain alone but deactivated during the cognitive task in the absence of pain. The S2 regions overlap greatly, whereas the mid insula regions lie adjacent to each other. Because of our limited resolution and use of group-averaged data, the S2/pIns activation we report could include both the nonpainful and painful stimulation–evoked action of S2 previously reported (Ferretti and others 2003; Eickhoff and others 2006). Several possible reasons for activations in these regions during the task exist. One possibility is that there was an increase in activity in response to a lack of stimulation after the rest period, in which pain was anticipated. Sawamoto and others (2000) demonstrated that posterior insula is activated by anticipation. Thus, during the preceding baseline period, activity in posterior insula could increase, then suddenly decrease when the task changed, but pain was not delivered. However, this explanation seems unlikely because the strength of the deactivation increased with increasing task difficulty. A second possibility is that this area is part of a default mode or a task-negative network (see Raichle and others 2001; Greicius and others 2003; Fox and others 2005), in which a task will result in a deactivation. In any case, because we showed modulation of S2/posterior insula without pain, it is important to consider this in interpreting the "modulation" of S2/pIns with pain by a cognitive task. That is, it may be that the decrease in activity reflects a deactivation in response to the task and not strictly an interaction between task and pain.

Conclusions

Our results indicate that the brain can support multitasking across perceptual and cognitive loads. That is, most pain-evoked and cognitive-evoked brain activity is robust. The data show that when subjects are instructed to engage in a task, the performance on that task is not affected by the presence of mild or moderate intensity pain and regional cognitive-related activity is minimally affected. On the other hand, pain-related brain activity can be reduced with cognitive engagement, but this reduction is modest and independent of task difficulty. The type of experimental design used here may be best suited to examine acute pain–cognition interactions, but a different model may be needed to study cognitive impairment associated with chronic pain. Future studies must address pain–cognition interactions with explicit questions and considering the role of pain belief and control.

Notes

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